

Assessment of variability and coordination of upper and lower body segments during walking in
healthy adults and persons with multiple sclerosis

BY

Jordan John William Craig

Submitted to the graduate degree program in Bioengineering, and the Graduate Faculty of the
University of Kansas, in partial fulfillment of the requirements for the degree of Master of
Science.

Chairperson: Dr. Jessie Huisinga

Dr. Carl Luchies

Dr. Sara Wilson

Date Defended: December 7th, 2015

The Thesis Committee for Jordan J.W. Craig certifies that this is the approved version of the following thesis:

Assessment of variability and coordination of upper and lower body segments during walking in healthy adults and persons with multiple sclerosis

Chairperson: Dr. Jessie Huisinga

Date Approved: December 7th, 2015

Abstract

Persons with multiple sclerosis often report problems with gait and general instability during walking, possibly due to the disease's disruption of sensorimotor function.

Understanding variability of upper and lower body segments during walking is fundamental for assessing gait and balance, fall risk, and identifying differences in variability between healthy control subjects and persons with MS may help uncover specific control strategies in the healthy dynamic system necessary for maintaining overall stability. The primary purpose of this study is to examine the relationship between movement of upper and lower body segments during walking in healthy adults and in persons with multiple sclerosis. Currently no studies have compared upper and lower segmental control in patients with MS with that of healthy controls during walking.

Forty patients with MS and forty healthy control subjects were recruited for gait assessment while wearing wireless inertial sensors. Wireless sensors were attached to the trunk and right foot and subjects walked on a treadmill at self-selected pace. Measures of linear (range, root mean square) and nonlinear (approximate entropy, sample entropy, Lyapunov exponent, recurrence quantification analysis %recurrence) variability were calculated from the acceleration time series recorded by the inertial sensors. Paired t-tests were used to test for differences due to location in healthy controls. Two two-way ANOVAs were used (one for the frontal plane and one for the sagittal plane) to test for main effect of group and main effect of sensor location on each of the variability measures. Pearson's correlations were applied to evaluate relationships between variability of acceleration at the trunk and at the foot within the frontal and sagittal planes. No main effect of group was found for any variability measures. Main effect of location was found for all variability measures, with magnitudes of variability

greater at the feet compared to the trunk and structure of variability showing more predictable variability patterns at the foot compared to the trunk. Significant correlations were found between trunk and foot accelerations in the frontal plane for RMS, range, ApEn, SaEn, and LyE, and in the sagittal plane for RMS, ApEn, SaEn, and RQA %REC in healthy controls. For persons with MS, significant correlations were found between trunk and foot accelerations in the frontal plane for RMS, range, and LyE, and in the sagittal plane for RMS, range, ApEn, and LyE.

The current study found that variability of upper and lower body segments was significantly altered in persons with MS compared to healthy controls. MS appears to affect the relationships between motion of the feet and motion of the trunk during walking indicating that underlying control mechanisms which govern gait stability may be altered in persons with MS. These control systems may be affected by the pathophysiology of MS, particularly the slowed conduction velocity in the neurons of the central nervous system which ultimately make up the wiring of these control systems. Examining relationships between upper and lower segment motion during walking may therefore be able to provide more relevant gait assessments across various populations, including those with neuromuscular disorders. Assessments based on these measures may ultimately provide therapists with a tool to measure gait stability and gait function.

Acknowledgements

First I would like to sincerely thank Dr. Jessie Huisinga for her encouragement, patience, enthusiasm, knowledge, and complete dedication to my training. It is difficult to explain how comforting it is to be pushed outside of my comfort zone so often, all the while knowing that each task I am given holds specific purpose and value for my training. I am incredibly proud of the work I have accomplished under her guidance. I would also like to thank Dr. Sharon Lynch for all of her assistance in the recruitment and screening of our study participants from within her Multiple Sclerosis clinic. I'd like to thank the Bioengineering graduate program at the University of Kansas, especially my committee members for their expertise and input. I would like to thank Adam Bruetsch, Molly Schieber, Sunny Ranu, Aly Reinholdt, Olivia Dykes, and the other members of the Human Performance Lab who have helped immensely in subject recruitment, data collections, data analysis, and allowing me time to regularly bounce ideas off of them. Lastly, I'd like to thank my wife, Sarah. Her support and encouragement constantly provides me with a solid foundation to tackle any challenges head on, and remind me of what is truly important.

Table of Contents

I.	Thesis Acceptance.....	1
II.	Abstract.....	3
III.	Acknowledgements.....	5
IV.	Table of Contents.....	6
V.	Table of Figures.....	9
VI.	Table of Tables.....	10
VII.	Table of Equations.....	11
VIII.	Introduction.....	12
	a. Statement of Hypothesis and Specific Aims.....	15
	i. Specific Aim One.....	15
	ii. Specific Aim Two.....	16
IX.	Review of Literature.....	17
	a. Background, Significance, and Rationale.....	17
	i. Control of Lower Body Motion During Walking.....	17
	ii. Control of Trunk Motion During Walking.....	20
	iii. Variability in Human Movement.....	23
	iv. Summary.....	28
X.	Research Design and Methods.....	29
	a. Summary of Research Methods.....	29
	i. Subjects.....	29
	ii. Inclusion and Exclusion Criteria.....	29
	b. Measures.....	30

i.	Experimental Apparatus.....	30
ii.	Experimental Measures.....	31
iii.	Linear Measures of Variability.....	32
iv.	Nonlinear Measures of Variability.....	33
c.	Experimental Protocol: General.....	37
d.	Experimental Protocol: Treadmill Gait.....	37
e.	Data Analysis and Interpretation for each Specific Aim: Statistical Analysis.....	37
i.	Specific Aim 1: Statistical Analysis.....	38
ii.	Specific Aim 2: Statistical Analysis.....	38
XI.	Results.....	40
a.	Specific Aim 1.....	40
i.	Specific Aim 1 (H1.1): Variability of Upper and Lower Segments in Healthy Controls.....	41
ii.	Specific Aim 1 (H1.2): Comparison Between Variability Measures for Healthy Controls and Persons with Multiple Sclerosis.....	42
b.	Specific Aim 2.....	48
i.	Specific Aim 2 (H2.1): Relationships Between Variability of Upper and Lower Segments in Healthy Controls.....	48
ii.	Specific Aim 2 (H2.2): Comparison Between Relationships of Variability Measures in Healthy Controls and Persons with Multiple Sclerosis.....	48
XII.	Discussion.....	50
a.	Specific Aim 1.....	50
i.	Hypothesis 1 (H1.1).....	50

ii.	Hypothesis 2 (H1.2).....	53
b.	Specific Aim 2.....	56
i.	Hypothesis 1 (H2.1).....	56
ii.	Hypothesis 2 (H2.2).....	58
c.	Limitations.....	63
XIII.	Conclusions.....	65
XIV.	Appendix.....	67
XV.	Literature Cited.....	135

Table of Figures

Figure 1: Illustration of structure of variability.....	24
Figure 2: Illustration of model for optimal movement variability.....	27
Figure 3: Subject wearing wireless sensors.....	31
Figure 4: Alignment of inertial sensor axes in anatomical reference planes.....	32
Figure 5: Example recurrence plots.....	36
Figure 6: Results of two-way ANOVAs in frontal and sagittal planes.....	47

Table of Tables

Table 1: Subject demographics.....	40
Table 2: Results of paired tests in frontal plane.....	41
Table 3: Results of paired tests in sagittal plane.....	42
Table 4: Results of two-way ANOVA in frontal and sagittal plane.....	46
Table 5: Correlations for variability measures.....	49

Table of Equations

Equation 1: Range.....	33
Equation 2: Root Mean Square.....	33
Equation 3: Vector for Entropy Analysis.....	34
Equation 4: Vector for Entropy Analysis.....	34
Equation 5: Equation to Calculate Approximate Entropy.....	34
Equation 6: Equation to Calculate Sample Entropy.....	34
Equation 7: Reconstructed State Space.....	35
Equation 8: Calculation of Lyapunov Exponent (Wolf's Algorithm).....	35
Equation 9: Calculation of Rate of Recurrence.....	37

Introduction – Chapter #1

1. A. Statement of Hypothesis and Specific Aims

The purpose of this study is to examine the relationship between movement of upper and lower body segments during walking in healthy adults and in persons with multiple sclerosis (PwMS). Acceleration patterns at the foot and trunk were measured in an effort to better understand how movement of these segments is coordinated to maintain stability during walking. Determining the relationship between movement patterns of the foot and of the trunk during walking in healthy adults and PwMS may identify group differences in segmental control which in turn may help develop more sensitive measures to monitor disease progression or identify persons at risk for falls.

Multiple sclerosis (MS) is a progressive inflammatory demyelination disorder that causes a breakdown of the myelin sheath that surrounds the neurons of the central nervous system (CNS), and affects an estimated 16.6 to 357.6 per 100,000 persons in North America [1]. The degradation of the myelin sheath disrupts the transmission of neuronal signaling in the CNS, resulting in decreased motor and cognitive function [2]. Common symptoms of MS include gait and balance deficits, cognitive impairment, fatigue, ataxia, muscle weakness, and depression [2]. These deficits can often lead to increased risk of falls, with between 52% and 63% PwMS reporting at least one fall in a 2 to 6 month period [3, 4]. Developing a more sensitive method of measuring stability would be highly advantageous for studying movement changes in research and clinical settings. Additionally, developing a method of monitoring movement outside of a laboratory, and in everyday life could provide much more relevant information for understanding instability during typical daily living across a wide variety of populations.

Understanding movement variability of the trunk and lower body segments during walking is fundamental for assessing gait and balance and fall risk and for identifying differences in variability between healthy control subjects and persons with MS may help uncover specific control strategies for maintaining overall stability. Acceleration patterns at the foot and at the trunk provide direct information about how those segments of the body move during gait. The feet act as the point of contact between the body and the ground during gait and therefore provide the body with its dynamically changing base of support during walking. Understanding the control strategies for foot motion and step placement is important to better understand how the body maintains a reliable base of support. Similarly, accelerations at the trunk provide information about motion at the trunk during walking, which essentially provides information on the motion of the center of mass. Center of mass motion is important as stability requires controlling the interactions between the base of support and the center of mass from step to step. Additionally, control of trunk motion is important for providing a stable base for the neck and head, which contains various sensory organs which are important for orientation and balance. Accelerations are attenuated from inferior to superior segments of the body during walking which helps keep the center of mass and the head stable, decreasing undesirable higher frequency accelerations [5]. A healthy sensorimotor system is able to achieve a gait pattern which optimizes these interactions through control mechanisms constantly providing feedback from step to step. However, impaired sensorimotor systems may not be able to optimally control these interactions for a variety of physiological reasons. Specifically in persons with MS, sensory reception may be compromised, nerve conduction velocities may be slowed, and motor control may suffer from increased muscle fatigue [6-8]. It is therefore important to examine the relationship between upper and lower body motion to better understand how the healthy adult

sensorimotor system controls stability during gait, and also how MS affects these relationships. Identifying how these relationships between upper and lower body segments during gait are affected in PwMS will assist in developing metrics such as a gait stability index or measures of fall risk.

Clinical or laboratory based assessments are often used to assess and monitor gait and balance deficits, with an overall goal of monitoring patient responsiveness to treatment or progression of disease. Current clinical assessments, such as the Berg Balance Scale, are often inexpensive and simple for trained professionals to administer and interpret. Laboratory based measurement tools such as force platforms and motion analysis systems offer very high levels of sensitivity but require expensive equipment and trained personnel to conduct analysis on specific gait and balance parameters. While clinical functional assessment is able to give a relatively objective balance performance score and possibly identify individuals at higher risk for falls, more sensitive and objective laboratory based measures are able to better differentiate between specific types of balance disorders [9]. Unfortunately, the use of laboratory based measures in a clinical setting is often not feasible, as the equipment is expensive and requires advanced training to use. However, advances in the use of small, wireless sensors may offer advantages and opportunity for use in clinical settings. Wireless sensors are relatively inexpensive compared to force platforms and motion analysis systems, but can be similarly used to measure a wide variety of gait and balance parameters with a high degree of sensitivity [10-12]. Using wireless sensors to examine accelerations of upper and lower body segments during walking may reveal complex control strategies of the dynamic system to maintain overall stability and efficiency [5, 13, 14].

Specific Aim #1: *To determine if variability of accelerations at the foot and at the trunk during walking differ between healthy control subjects and persons with MS through the use of wireless sensors.*

Utilizing both linear and nonlinear measures of acceleration variability can provide information about the cyclical motion at the foot and trunk during walking. By employing wireless sensors, researchers and clinicians could gather objective information related to segmental control in virtually any setting or population.

H1.1. It is hypothesized that healthy control subjects will display lower magnitudes of variability, and a higher degree of regularity at the trunk compared to the feet. During walking, accelerations are attenuated inferior to superior segments in the body, which we expect will also lead to lower magnitudes of variability in the trunk compared to the foot [5]. As the central nervous system aims to keep the body's center of mass stable during walking, we expect to see a different structure of variability in accelerations at the foot compared to the trunk as step placement will be constantly altered to maintain stability throughout the walking cycle.

H1.2. It is hypothesized that PwMS will exhibit different amounts and structure of variability for foot and trunk accelerations during walking, compared to healthy control subjects. Previous studies have shown that PwMS display altered variability patterns, which may be representative of less adaptability during walking. Therefore, we expect to see different patterns of variability in accelerations at the trunk and at the feet during walking in PwMS compared to healthy control subjects.

Specific Aim #2: To determine the relationship between upper and lower segmental motion represented by acceleration patterns of the foot and of the trunk in healthy control subjects and PwMS.

Examining acceleration patterns at the foot and at the trunk during walking in healthy adults and PwMS may uncover important differences in the methods of stability control employed by these two populations. Understanding segmental control differences in PwMS could help to better understand fall risk.

H2.1. It is hypothesized that a relationship will exist between variability of accelerations at the feet and at the trunk during walking in healthy control subjects. As lower body segments are mechanically tied to upper body segments, we expect that increased variability in accelerations at the feet will be reflected in increased variability in accelerations at the trunk [15, 16].

H2.2. It is hypothesized that the strength of relationships between variability of accelerations at the feet and at the trunk during walking will be different in PwMS and healthy control subjects. Previous studies have shown that PwMS display altered variability in walking parameters [10, 17, 18]. If foot motion and trunk motion are highly dependent on each other, perturbations in one will cause perturbations in the other, and the system cannot easily compensate between the two segments. In PwMS, the feedback system responsible for responding to perturbations may be altered, requiring a different control strategy compared to HC [6].

Review of Literature – Chapter #2

1. B. Background, Significance, and Rationale

B. 1. Control of lower body motion during walking

Walking requires coordination between the lower extremities, the trunk, the head, and the upper extremities. The traditional major determinants of gait – pelvic rotation, pelvic tilt, knee flexion in mid-stance, foot and ankle motion, knee motion, and lateral pelvic displacement – are all associated with the segments of the lower extremity [19]. Control of these lower body segments is fundamental to maintaining a reliable base of support from step to step, which is critical for whole body stability. A lack of stability effectively means that someone is at risk for falls [20-23].

Studies examining the maintenance of stable gait in simplified models have shown that motion in the sagittal plane can be maintained step to step via relatively passive mechanisms [16, 24]. However, movement in the frontal plane, including step width and frontal plane tilt may require a greater degree of active control by a feedback system to maintain stability [16]. Efficient control schemes for the maintenance of frontal plane stability are thought to act to adjust step width during the gait cycle in reaction to perturbations such that subsequent steps realign with the normal and preferred trajectory [16]. As motion in the sagittal and frontal planes may be controlled via separate strategies, it is important to examine motion in these planes individually to uncover information about each of these strategies, and how the strategies may be affected in PwMS. Therefore, examining the relationships between upper and lower segmental accelerations in order to understand how the segments are coordinated to maintain stability should involve examining both the frontal and sagittal planes.

Previous work examining frontal plane motion has shown that a lack of stability in the frontal plane is commonly associated with increased risk of falling and is often characterized by significantly altered step width and step width variability [25-27]. Bauby and Kuo identified the frontal plane to likely require active feedback mechanisms during walking [26]. In populations, such as PwMS, who have walking and balance deficits and who are at higher risk for falls [3, 4], it is possible these control mechanisms may be damaged or deficient due to decreased proprioception, increased sensorimotor delays, and decreased muscle strength [6, 10, 26, 28, 29]. Individuals who express difficulty in maintaining frontal plane stability may adopt a gait strategy with a relatively wide step width to essentially increase their base of support [18, 30]. Healthy adults in general may have individualized strategies for maintaining stability in a destabilizing environment [31]. In other words, the stabilization strategy may be less important than the outcome. However, there may be times when certain stability strategies should be encouraged or discouraged due to the strategy's inherent safety or energy efficiency. This can be especially important in PwMS and other populations with known stability deficits, who often adapt to their disability by walking more slowly or by taking shorter steps in order to decrease fall risk. Identification of specific differences in movement patterns of the feet and trunk between healthy adults and PwMS is needed to begin identifying stability strategies which should be encouraged. Frontal plane instability in particular may result from a step width which was not sufficiently wide enough to redirect the body's center of mass appropriately in time for the subsequent step [32]. Based on this conclusion, it is important to explore not only lower body motion, but its relationship and coordination with upper body motion in maintaining stable gait. Unfortunately, step width is not easily measured outside of a gait laboratory. However, wireless sensors have

been used to measure a variety of spatio-temporal parameters of gait, and may be useful as a gait analysis tool [33-35].

The sagittal plane is the primary plane of motion during gait so step length is a primary parameter chosen by the system to optimize energy cost, walking speed, and cadence while minimizing vertical and anterior-posterior motion of the head and pelvis [36, 37]. Therefore, adjusting step length is fundamental to steady state walking and can be maintained by relatively passive mechanisms during walking [26]. When subjects are asked to avoid obstacles while walking on a treadmill, adjustments to lengthen a step were easier than adjustments to shorten or widen a step [38]. The benefit of step lengthening for adjusting step placement is that it allows more time to make adjustments during the swing phase compared to step shortening which abruptly stops the stepping motion and requires antagonistic muscle activation to arrest the body's momentum [38]. Step shortening in order to avoid an obstacle may be particularly difficult for PwMS due to muscle weakness and slowed sensorimotor responses [6, 28].

Examining lower body motion alone limits the ability to fully describe total body control during walking. Stability measures, step kinematics, and trunk kinematics provide important but individual information about the success of a compensatory response to a disturbance during walking [39]. However, as studies typically focus on motion of the feet or motion of the trunk separately, the relationship between movement patterns at the feet and the trunk remains unclear.

It is important to further investigate the relationships between lower and upper body motion during walking, as stable gait involves the coordination of upper and lower body segments. Examining the variability of footfall variables alone does not allow for one to draw conclusions about the stability of someone's gait, as stable gait is a function of upper and lower body segments [40]. Without relating motion at the feet to the motion at the trunk, it is difficult

to interpret spatial and temporal footfall results in terms of full body stability. Linear variability measures of step length and step time have been found to be higher in PwMS compared to HC [18]. Nonlinear variability measures have shown that PwMS exhibit more regular and repeatable patterns of step length and step width, which may be indicative of a reduced ability for the system to adapt and react to perturbations [17]. However, as these findings have been based only on footfall data, the control strategies related to whole segment motion that are employed to maintain whole body stability during walking remain unknown. Although temporal parameters of gait events such as step time and swing time can provide objective information about asymmetries and general level of functional mobility [41, 42], spatial parameters provide further detail about the movement during the gait cycle [12, 34, 43]. In fact, foot acceleration recorded by wireless sensors showed significant differences between a fall prone group and a healthy control group [21]. However, the assessment was shown to be more powerful when the walking foot acceleration analysis was coupled with an analysis of trunk accelerations during a standing condition [21].

B. 2. Control of trunk motion during walking

The body's center of mass is generally located in the lower half of the trunk, but shifts as the various segments of the body move during gait [44]. During standing, balance is maintained by keeping the center of mass within the body's base of support [40]. However, during gait, the center of mass leaves and reenters the base of support during each individual step [40, 45]. Balance during gait is maintained by controlling the interaction between the base of support and center of mass [45]. Therefore, investigating the relationship between foot motion and trunk motion can provide information critical to understanding whole body control and balance during walking. Elderly subjects with a previous history of falls elicited a more conservative gait

pattern which aimed to keep their center of mass closer to their base of support compared to healthy younger subjects [45]. However, while persons at risk of falls are often trained to adopt a more conservative gait pattern [46], older adults who maintained a more conservative gait compared to younger adults may also have reduced ability to attenuate accelerations within the trunk segment, leading to greater mediolateral head jerk which may disturb orientation and balance sensory organs and increase fall risk [13, 47]. Therefore, while some current training goals may aim for individuals at risk of falling to adopt a more conservative gait, this may not result in greater whole body stability. Further understanding of how stability is maintained during walking may help develop assessment strategies able to target and subsequently train persons at risk of falling.

Understanding trunk motion in addition to foot motion is important to better understanding relationships between foot placement and center of mass motion, as well as understanding the role the trunk plays in maintaining stability and sensorimotor integrity during walking. As walking speed increases, trunk sway and lateral oscillations of the center of mass decrease while vertical oscillations increase [48]. Stabilizing the upper body during gait is essential for keeping an upright posture, diminishing fall risk, and controlling head movements to maintain effective processing of information from the visual and vestibular systems [13]. The vestibular and visual systems play a major role in regulation of gait and balance by giving constant feedback about speed, tilt, direction, and environmental factors. An inability to stabilize the head during gait may result in an increased fall risk due to an unstable visual field [13, 49]. To address the goal of stabilizing the head, the body must counteract the large magnitudes of acceleration originating from the lower body segments during gait. Previous studies have shown that accelerations are attenuated from inferior to superior locations in the trunk during walking

[5, 49-51]. The regulation of accelerations within the trunk offers significant advantages as high frequency oscillations are attenuated prior to reaching the sensitive sensory receptors related to stability and orientation of the head [52]. To attenuate accelerations and stabilize the neck and head, the trunk actively controls spinal muscles while passive mechanical dampening also occurs through the tissue structures [51, 53]. However, studies have shown that a compromised sensorimotor system may hinder trunk control and attenuation of accelerations [14, 54].

Acceleration time series recorded at the trunk during walking can provide valuable information about the state of the motor control system during walking [34]. For example, the amount and structure of variability of accelerations of the trunk during walking was altered in PwMS compared to healthy control subjects [10]. To account for an inability to attenuate accelerations through the trunk, elderly adults couple the motions of the head and trunk which provides a more stable reference frame but reduces independent control between segments [14]. While this may increase stability of the head, this reduces flexibility within the system which may inhibit reactions to perturbations and cause a decrease in overall stability during walking [14, 55]. Of significant importance in the current study is examining how performance of the trunk segment impacts overall stability, and whether suboptimal performance evokes a compensatory control strategy of lower body segments. While healthy older adults do exhibit significant differences in the motion of upper and lower segments during walking compared to healthy young adults, trunk motion displays the greatest difference between older and younger adults [56]. Transtibial amputees, however, were able to maintain trunk motion similar to able-bodied control subjects but lower body motion was significantly different compared to the able-bodied control subjects [57]. It is not clear how the relationship between upper and lower body motion is defined across different populations, and how this relationship is affected in individuals with a known

sensorimotor deficit, including PwMS. Measures of trunk sway were more sensitive to the presence of functional deficits in PwMS than some clinical assessments [54], providing support for the development of more objective assessments to directly measure trunk motion or whole body motion during walking.

B. 3. Variability in human movement

Variability in human movement and motor control may offer important information about the state of an individual's sensorimotor system. There appears to be healthy levels of variability, and therefore altering variability either by increasing or decreasing compared to healthy populations, may not be optimal [58, 59]. Variability of movement in both the trunk and in the lower extremities has shown to be altered in pathological populations [10, 59-63]. However, the relationships between variability of upper and lower body motion is not well understood.

Linear measures of variability give information about the magnitude of variability within a time series, and are essentially measures of random error around a mean. In other words, a larger root mean square would indicate more random errors between repetitions of a task, assuming variations between repetitions are independent of previous and future repetitions. However, previous motor control studies have shown that this variability often displays non-random characteristics, possibly evidence of underlying control mechanisms (Figure 1) [60, 64, 65]. Walking provides a simple illustration of this, as there is typically variation in step width from step to step which seems random, however any variation in one step will influence the subsequent steps, thus driving an underlying temporal structure to the variability. While linear measures of variability can provide information on how much variability is present in a system,

there is relevant information embedded in the temporal structure of time series which can be measured by nonlinear measures of variability.

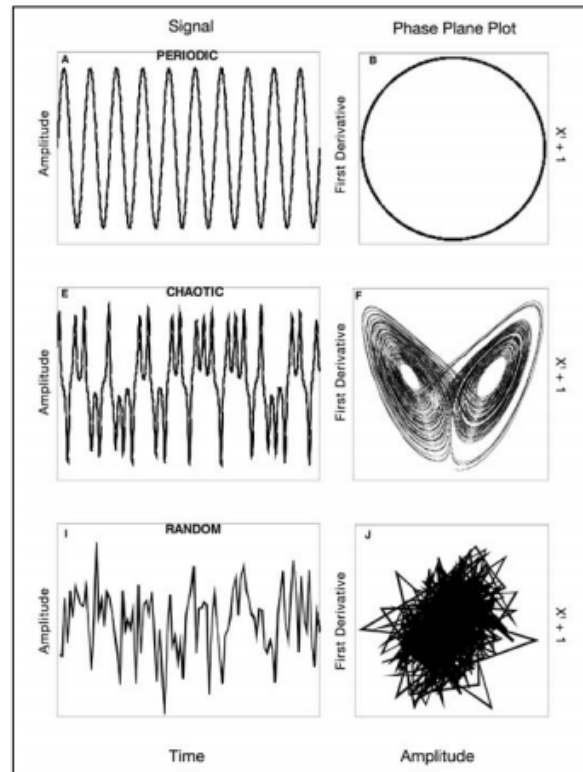


Figure 1. Showing periodic (top), chaotic (middle), and random (bottom) time series all with a mean of 0 and standard deviation of 1.0, and their respective phase plane plots to illustrate the existence of non-random structure embedded in variability .

Nonlinear measures of variability quantify the temporal structure of variability in a time series. A commonly used measure of nonlinear variability is the Lyapunov exponent (LyE), which is a measure of local dynamic stability. Local dynamic stability refers to the ability of the system to correct for any small perturbations [60]. It is important to recognize that dynamic stability refers to measurement of the stability of a specific time series, and not a direct measurement of the overall stability of a person. Nonetheless, there is substantial evidence for the usefulness of LyE in understanding human movement variability. During walking, the magnitude of variability within subjects' trunk motion follow a U-shaped curve with the least

amount of variability at the subjects' preferred walking speed [66]. However, in this study and a similar study by England and Granata, dynamic stability (LyE) was greatest at the lowest walking speed, and subsequently decreased as subjects walked faster [66, 67]. The findings of this study seem to provide support that individuals should walk more slowly to increase their stability, even at the cost of increasing overall magnitudes of variability [66]. However, these studies only looked at the mathematical stability of time series recorded from single points on the body during walking, and it is therefore difficult to draw conclusions about whole body stability from these results. Examining local dynamic stability in superior and inferior segments simultaneously can uncover further information about the system. Kang and Dingwell examined LyE of upper and lower body segments during walking, and found that superior segments were much less susceptible to small perturbations compared to inferior segments [56]. LyE also identified differences between control of walking in older and younger adults, as older adults exhibited lower dynamic stability across all segments compared to younger adults [56]. Many studies have found that decreased dynamic stability is tied to fall risk, and therefore LyE may be useful in identifying or quantifying fall risk or gait abnormalities [21, 23, 68]. The current study aims to examine dynamic stability between upper and lower body segments during walking, specifically investigating how dynamic stability at the feet is related to the trunk which may uncover whole body control mechanisms during walking.

This increase in regularity among the older adults and persons with knee osteoarthritis follows a principle known as the “loss of complexity” hypothesis within the theory of optimal movement variability (Figure 2). The theory explains that there is a level of optimal (healthy) variability or complexity which signifies the adaptability of a physiological system [59]. A decrease in this healthy variability may be a characteristic of pathology, and the system either

becomes more random or more predictable and inflexible [59]. It is accordingly of interest to examine differences in the structure of acceleration patterns during walking in healthy controls and PwMS. Gaining a better understanding of relationships between how motion is controlled at the feet and at the trunk requires inspection of multiple nonlinear measures, as each measure may relate to different aspects of the sensorimotor system.

Walking is a highly cyclic activity, as the overall patterns of motion repeat with each gait cycle. To examine how tightly controlled a cycle is, one can measure its regularity or periodicity. For example, a sine wave is completely regular and periodic, and would have virtually no variability between cycles. Measures of entropy such as approximate or sample entropy are measures of complexity of a time series, and are able to quantify the time series' regularity or periodicity. Sample entropy has been used to analyze acceleration time series recorded from sensors placed on the leg, and was able to detect a higher degree of regularity in older adults compared to younger individuals [63]. Additionally, individuals with knee osteoarthritis elicited more regular patterns of leg motion compared to age-matched healthy control subjects [63]. Entropy measures show differences between walking speeds, as trunk accelerations have been shown to be less regular at slower walking speeds compared to preferred walking speed [69]. This is seemingly in contrast to the variability trends seen with LyE, where slower walking speeds increased the local dynamic stability [66]. However, while regularity and dynamic stability both measure nonlinear variability, it is important to note that they measure different aspects of the variability, with dynamic stability measuring the predictability of the time series, and entropy measuring the regularity of the time series. Ultimately, it is important to take into account the different variables being measured, and identify the clinical relevance for each of these types of variables.

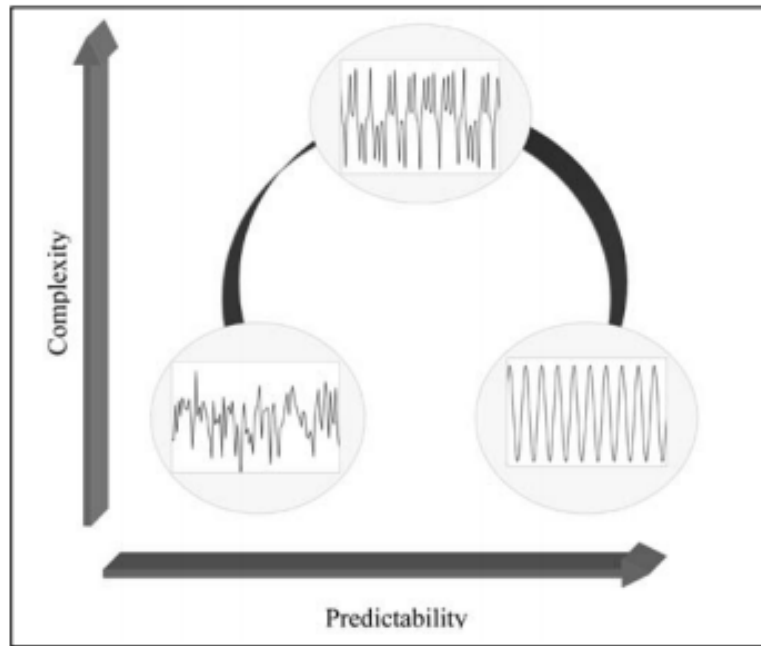


Figure 2. *Illustrating the theoretical model of optimal movement variability. Proposed healthy variability is characterized by high complexity [59].*

A principle application in assessment of gait stability is to identify individuals at risk of falling. LyE has shown promise in being able to identify individuals at risk of falls [21-23, 70]. Similarly, entropy measures have shown the potential to be used in fall risk assessment and an ability to identify subtle difference in gait including segmental control and regularity [63, 69, 71]. A third nonlinear measure, recurrence quantification analysis (RQA), has also shown promise in being able to determine persons who have previous history of falls and persons who have decreased stability [72, 73]. RQA is specifically of interest when examining how tightly controlled a pattern is, as it can identify the existence of a repeating pattern throughout the entire length of a time series. This could be specifically useful when making inferences on the sensorimotor system's ability to reproduce a specific movement pattern repeatedly. Similarly cross recurrence quantification analysis can be used to examine patterns reflected between two

different time series, which provides useful information about the coupling occurring between two separate systems [74], such as the coordination between foot motion and trunk motion to maintain over stability during gait. Combining linear and nonlinear variability measures offers a significantly more robust understanding of the data by explaining not only how much variability is present in the system, but underlying patterns and structures of the variability which may be related to driving mechanisms in the system itself.

B. 5. Summary

The purpose of this study was to examine relationships between movement coordination of upper and lower body segments during walking in healthy adults and PwMS using wireless sensors which have the potential to be highly beneficial for clinical and home assessment of mobility function. By examining upper and lower body segmental motion simultaneously, it should be possible to determine specific relationships and levels of coordination necessary to maintain stable healthy gait. Comparing the relationships of segmental coordination between healthy controls and PwMS will help identify which relationships may play a prominent role in maintaining stability, and any effects MS has on these relationships. The identification of these relationships between upper and lower body motion will ultimately help to develop more sensitive metrics such as a gait index to be used as a highly sensitive functional mobility assessment. Development of these sensitive and easy to use tools should allow for increased efficiency and efficacy of treatment protocols, which will ultimately improve quality of life for individuals with MS and perhaps other known causes of gait and balance deficits.

Methods – Chapter #3

1. C. Research Design and Methods

1. C. 1. Summary of Research Methods

1. C. 1a. Subjects

The study consisted of two groups: subjects with MS (n=40) and a group of healthy controls (n=40) who were matched for age to the subjects with MS. Healthy control subjects were recruited from the community. Subjects with MS were recruited through the MS Clinic at the University of Kansas Medical Center with the assistance of Dr. Sharon Lynch, MD. In addition to indicating disease history and performing a general neurological evaluation, Dr. Lynch administered a complete Expanded Disability Status Scale (EDSS) evaluation for each subject. The participating subjects in this study were given informed consent prior to their general neurological examination administered by Dr. Lynch, while healthy control subjects were given informed consent by the one of the secondary investigators at the time of data collection appointment.

1. C. 1b. Inclusion and Exclusion Criteria

Forty subjects with MS between the ages of 20 and 60, and forty age matched healthy control subjects were recruited for this study. Healthy control subjects were screened during the consent process, and were free of any known neurological or musculoskeletal pathology or disorder which would have an adverse effect on the participant's balance or gait. Subjects with MS who were prescribed symptom specific medication therapies (i.e. Fampridine) were restricted from participation due to its direct effect on gait. Although no specific MS subtypes were excluded, individuals with an EDSS greater than 5.5 or participants unable to walk a distance of 25 feet without the assistance of a mobility aide were not included in the study. All

participants with MS had relapsing-remitting MS. Additionally, subjects from either sample population were excluded if they presented with any neurological or orthopedic co-morbidities possessing the potential to alter balance or gait mechanics. Female subjects who were pregnant, breastfeeding, or within 3 months post-partum at the time of data collection were also not included in the study. Individuals with vestibular issues, diabetes, or a pre-existing condition which could make exercising difficult (i.e. myocardial infarction, chest pain, unusual shortness of breath, congestive heart failure, etc.) were also not included in the study. All screening documents used in the current study can be found in the appendix.

1. C. 2. Measures

1. C. 2a. Experimental Apparatus

Data collections were conducted at the Human Performance Laboratory (HPL) located within the Landon Center on Aging at the University of Kansas Medical Center (KUMC). Acceleration data was recorded at 128Hz through the use of two APDM wireless sensors (Opal, APDM, Portland, OR, USA) secured by elastic strap to the right ankle and trunk as shown in Figure 3. The trunk accelerometer was placed over the midline of the sternum, inferior to the manubrium and superior to the xiphoid process. The right ankle accelerometer was placed over anterior surface of the lower shank, on the distal most point of the shank, superior to the ankle joint such that dorsiflexion of the foot would not cause any disturbance to the position of the sensor. Previous studies have shown that accelerations are attenuated inferiorly to superiorly within the trunk segment [51], therefore we chose to place the trunk accelerometer over the sternum rather than the lumbar spine in order to measure what is theoretically the more stable position on the trunk. Subjects proceeded to walk on a motorized treadmill (Woodway Bari-Mill, Eugene, OR, USA) at self-selected comfortable pace for 3 minutes.



Figure 3: Subject wearing the trunk sensor and ankle sensor.

1. C. 2b. Experimental Measures

The raw acceleration time series were exported to Matlab (MATLAB version R2013b, The MathWorks, Inc., Natick, Massachusetts, USA) and were initially translated from local 3-dimensional Cartesian coordinates to resultant frontal and sagittal plane time series. These resultant frontal and sagittal plane time series were not aligned to the global anatomical planes, but only local to the individual sensors. The frontal plane time series was formed from the resultant of the X and Y acceleration time series, while the sagittal plane time series was formed from the resultant of the X and Z acceleration time series (Figure 3). All subsequent processing took place on the resultant frontal and sagittal acceleration time series. Matlab code for approximate entropy, sample entropy, and Lyapunov exponents was adapted from code

developed by John McCamley and the University of Nebraska Omaha Center for Research in Human Movement Variability [75, 76]. Matlab code for recurrence quantification analysis was adapted from code developed by Bruce Kay (University of Connecticut) and Michael Richardson (University of Cincinnati). For accurate analysis of the variability and complexity within the time series, data was left unfiltered [77].

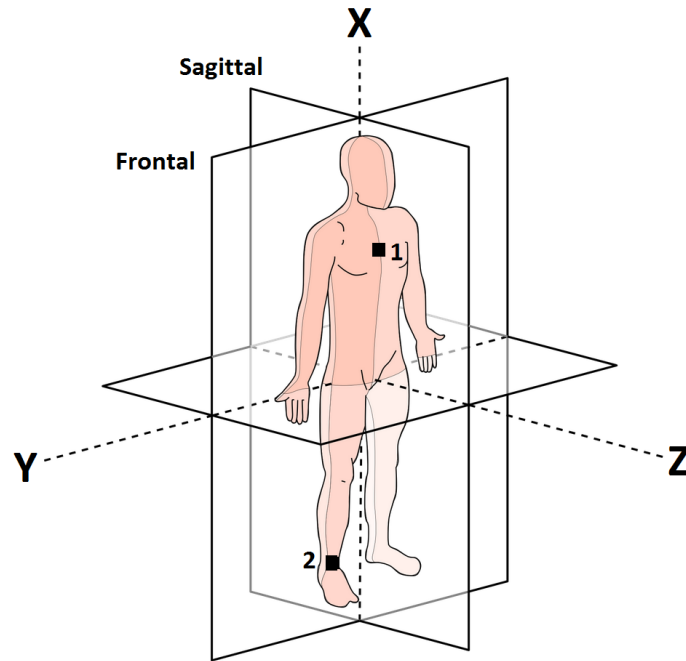


Figure 4. *Alignment of axes from inertial sensors 1 (trunk sensor) and 2 (right ankle sensor) with anatomical planes.*

1. C. 2b1. Linear Measures of Variability

Range: A custom Matlab program was used to calculate the range of both the frontal and sagittal plane unfiltered acceleration time series. Range was used to quantify the absolute spread of the acceleration time series recorded during the trials.

$$Range_{Frontal/Sagittal} = Max(Acc_{Frontal/Sagittal}) - Min(Acc_{Frontal/Sagittal}) \quad \text{Eq. (1)}$$

Root Mean Square: A custom Matlab program was used to calculate the root mean square (RMS) of both the frontal and sagittal plane unfiltered acceleration time series. RMS was used to quantify the dispersion of the acceleration time series recorded during the trials.

$$RMS_{Frontal/Sagittal} = \sqrt{\frac{\sum Acc_{Frontal/Sagittal}^2}{N}} \quad \text{Eq. (2)}$$

1. C. 2b2. Nonlinear Measures of Variability

Entropy: A custom Matlab program was used to calculate approximate entropy (ApEn) and sample entropy (SaEn) and of both the frontal and sagittal plane unfiltered acceleration time series. ApEn (m, r, N) and SaEn(m, r, N) quantifies the entropy in a time series consisting of N data points, and is defined as the negative natural logarithm of the probability that a vector, or sequence, of data points of length, m , would repeat itself at $m+1$ [75]. Time lag, τ , is not typically included in entropy algorithms as $\tau=1$ is typically sufficient [75, 78]. However, it was appropriate in the current study to use a time lag was to account for the accelerometers' high sample rates, differences in relative accelerations and magnitudes between the sensor at the foot and the sensor at the trunk, and to quantify the complexity of the signal due to nonlinear processes in the system [78]. The time lag was found by using the first minimum found by the average mutual information (AMI) algorithm [79]. Further details on the AMI algorithm can be found in the appendix. The principle behind finding the appropriate time lag is that a data point should have new information compared to the previous data point, but the points should not be so far separated from each other that they are completely independent of each other.

Given the raw acceleration time series, a set of m -length vectors, X_i was created such that the first vector contained data points 1 through m , as shown in Eq. (3). X_j was similarly created as shown in Eq. (4). Comparisons were then made against each m -length vector, X_i and X_j for $j=i+1$, for the length of the time series.

$$X_i = (x_i, x_{i+\tau}, x_{i+2\tau}, \dots, x_{i+(m-1)\tau}) \quad \text{Eq. (3)}$$

$$X_j = (x_j, x_{j+\tau}, x_{j+2\tau}, \dots, x_{j+(m-1)\tau}) \quad \text{Eq. (4)}$$

If the two vectors being compared fell within a predetermined tolerance level, $\pm r$ *standard deviation, the vectors were considered to be alike. The sum of the total number of alike vectors was then divided by $N-m+1$ and called B . The entropy algorithms then repeated this process but increased the vector length to $m+1$, and this subset was called A . ApEn was then calculated as shown in Eq. (5).

$$ApEn(m, r, N, \tau) = \frac{\ln(A)}{B} = \frac{\sum_{i=1}^{n-m\tau} \ln(A_i)}{\sum_{i=1}^{n-m\tau} B_i} \quad \text{Eq. (5)}$$

SaEn was then calculated as shown in Eq. (6).

$$SaEn(m, r, N, \tau) = -\ln\left(\frac{A}{B}\right) = -\ln\left(\frac{\sum_{i=1}^{n-m\tau} A_i}{\sum_{i=1}^{n-m\tau} B_i}\right) \quad \text{Eq. (6)}$$

A tolerance coefficient of $r=0.2$ was used in this study, making the tolerance level 0.2 *standard deviation, which is a general standard for entropy analysis. However, when using entropy measures, especially with continuous and cyclic time series data, it is important to examine the relative consistency of the analysis [80]. To check for relative consistency, the analysis was also run for vector lengths $m=2$ and $m=4$, as well as for tolerance coefficients $r=0.15$ and $r=0.25$. A perfectly regular and periodic time series such as a sine wave will result in a SampEn value of 0, and a random time series such as white noise will result in a SampEn value toward infinity.

Lyapunov Exponent: Local dynamic stability of the acceleration time series were assessed using the maximum finite-time Lyapunov exponent (λ_{\max}) found via Wolf's algorithm [76]. The first step required when calculating local dynamic stability is the reconstruction of the state space $Y(t)$. $Y(t)$ is a function of the time series data $x(t)$ which requires two main input parameters of time lag τ and an embedding dimension n , such that:

$$Y(t) = [x(t), x(t + \tau), x(t + 2\tau), \dots, x(t + (n - 1)\tau)] \quad \text{Eq. (7)}$$

Time lag is again found through the use of the AMI function, while the embedding dimension is found using the false nearest neighbors (FNN) approach [81]. Further details regarding the FNN algorithm can be found in the appendix.

The time series were then unfolded into the newly reconstructed state spaces, and λ_{\max} was then calculated for each time series. λ_{\max} measures the rate at which nearby orbits converge or diverge. The algorithm first chooses a random initial point and follows the subsequent points, creating a reference trajectory. The nearest neighboring vector is then selected which follows a second trajectory. The distance between these two vectors are $L(t_0)$ and $L'(t_1)$ after a given time evolution of t_1 . A new nearest neighboring vector is found nearest to the point on the reference trajectory at t_1 . $L(t_1)$ is the distance between the reference trajectory and this nearest vector.

This process is repeated until the reference trajectory has passed over the entire data set, with M being the total number of replacement steps. Then, λ_{\max} is then calculated by Eq. (8):

$$\lambda_1 = \frac{1}{t_M - t_0} \sum_{k=1}^M \log_2 \frac{L'(t_k)}{L(t_{k-1})} \quad \text{Eq. (8)}$$

The process is then repeated once for each embedding dimension, until you have a set of λ_m , one for each embedding dimension. The maximum exponent is then taken as the largest λ from this set. An exponent $\lambda > 0$ indicates exponential growth or divergence, $\lambda = 0$ indicates a marginally stable state, and $\lambda < 0$ indicates exponential decay or convergence.

Recurrence Quantification Analysis: Recurrence quantification analysis (RQA) provides information about the nature of repetitions within a time series, and can help answer questions about whether a system repeats itself over multiple iterations. A primary outcome of RQA is the recurrence plot, which allows for a simple visual analysis of how often and when a time series recurs over time. A recurrence plot is created by first finding the embedding dimension and time lag, via FNN and AMI explained above, reconstructing the state space, and then plotting the reconstructed time series against itself. When plotting the time series against itself, a dot is placed on the plot anytime there is similarity between the two time series (Figure 3).

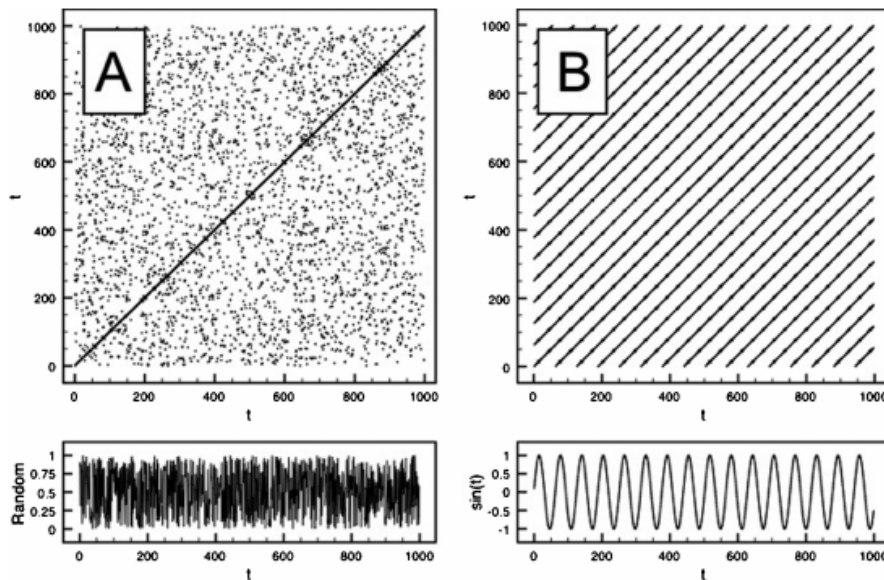


Figure 5. Recurrence plot examples of random noise (A) and a sine wave (B) [82] .

Finally a radius must be defined, which is a tolerance to indicate how similar points must be to be considered recurrent. This results in the obvious diagonal line indicating that the time series equals itself (i.e. $y=x$). However, other diagonal lines off of center may also appear, which identify times at which a pattern appears more than once in the time series. The rate of

recurrence is a measure which quantifies how often the system revisits the same state space, and is calculated by Eq (9).

$$RQA \%REC = \frac{\# \text{ of recurrent points}}{\text{Total \# of possible points}} \quad \text{Eq. (9)}$$

1. C. 3. Experimental Protocol

Every data collection was conducted at the Human Performance Laboratory on the University of Kansas Medical Center campus. Upon arrival, the subjects' height and weight were subsequently recorded. The subject was then fitted with two opal wireless inertial sensors affixed to the right ankle and upper trunk. Subjects with MS were then fitted into a safety harness, and stepped up onto the treadmill, at which time the harness was fastened to the ceiling. Healthy control subjects did not wear the safety harness during testing.

1. C. 3a. Protocol

Subjects were asked to begin walking as the treadmill was slowly increased in speed by the investigator. Subjects were instructed to notify the investigator when they felt they were at a comfortable walking pace which they could hold for 3 minutes. At this time, walking speed was recorded and subjects were instructed to continue walking, and acceleration data was collected for a single full 3 minute trial at the subjects' chosen walking speed. Since the average walking speed between groups was not significantly different, accelerations were not normalized to walking speed.

1. C. 4. Data Analysis and Interpretation for each Specific Aim

1. C. 4a. Statistical Analysis

All analyses were completed on the four individual time series separately: foot acceleration in the frontal plane, foot acceleration in the sagittal plane, trunk acceleration in the frontal plane, trunk acceleration in the sagittal plane.

1. C. 4a1. Specific Aim #1

Data from each plane was analyzed separately to investigate differences between the motion at the sensor locations and between groups.

H1.1. Paired t-tests were performed to examine differences in variability of accelerations between the 2 locations (foot and trunk) in the frontal and sagittal planes for HC. Mann-Whitney U tests and Signed-rank tests were used to investigate differences in RQA %REC, as the results were not normally distributed.

H1.2. A two-way ANOVA was performed to investigate effects of Group (HC, PwMS) and Location (foot, trunk), as well as any significant interaction (group, location). Separate ANOVAs were performed for the frontal and sagittal planes. Mann-Whitney U tests and Signed-rank tests were used to investigate differences in RQA %REC, as the results were not normally distributed.

1. C. 4a2. Specific Aim #2

Data was analyzed to evaluate the relationship between acceleration variability at the foot and trunk.

H2.1. Pearson's correlation coefficients were calculated for each variability measure between sensor locations, within the same anatomical plane, in order to determine if a relationship exists between variability of accelerations at the feet and variability of accelerations at the trunk during walking in healthy control subjects. Spearman's correlations were used for RQA %REC results, as the results were not normally distributed.

H2.2. Pearson's correlation coefficients were calculated for each variability measure between sensor locations, within anatomical planes, in order to determine if a relationship exists between variability of accelerations at the feet and variability of accelerations at the trunk during walking in persons with MS. Correlation coefficients were compared between healthy control subjects and persons with MS. Spearman's correlations were used for RQA %REC results, as the results were not normally distributed.

Results – Chapter 4

1. D. Specific Aim #1

The goal of the study's first specific aim was to determine if variability of accelerations at the foot and at the trunk during walking differ between healthy control subjects and persons with MS through the use of wireless sensors. Forty healthy control subjects and forty persons with MS were recruited for study participation. Based on total number of variability analysis results, approximately 10% of data points were identified as outliers and excluded from statistical analyses. Outliers were identified as data points which fell beyond the 1.5 interquartile range, as indicated by SPSS.

Group demographics and preferred walking speeds are shown in Table 1. Preferred walking speed appeared to be slightly slower in PwMS compared to HC, however this difference did not reach significance ($p = 0.065$).

Table 1: Description of demographics for healthy control subjects and persons with MS. *
significance < 0.05

	HC Mean (St. Dev)	PwMS Mean (St. Dev)	<i>P - value</i>
Gender	35 females	34 females	--
Age	44 (10) yrs	44 (9) yrs	= 0.962
Age range	20 - 58	21 – 57 yrs	--
EDSS	--	1.63 (0.7)	--
BMI	26.06 (4.6)	28.18 (6.7)	= 0.036 *
Preferred walking speed	1.01 (0.34) m/s	0.88 (0.23) m/s	= 0.065

1. D. 1. Specific Aim #1: Hypothesis 1 (H1.1)

The first hypothesis of specific aim one is focused on determining if variability of accelerations during walking differ between upper and lower body segments in the frontal or sagittal planes in healthy control subjects. Complete results can be seen in Tables 2 and 3. During walking, HC subjects demonstrated larger magnitudes of variability in accelerations at the foot compared to the trunk. Measures of entropy showed that accelerations are more regular at the foot compared to the trunk. Lyapunov exponents showed greater time series stability at the trunk compared to the foot. RQA %Determinism showed that accelerations at the trunk are more deterministic (more predictable) at the trunk compared to the foot, though this result reached significance in the frontal plane only.

Table 2: Results of paired t-tests performed on variability measures for acceleration at the foot and trunk in the frontal plane during walking in healthy controls; * significant difference between locations.

Frontal Plane		Trunk Mean (St. Dev)	Foot Mean (St. Dev)	Significance <i>T</i> statistic (<i>p</i>-value)
Linear	RMS	1.646 (0.421)	5.033 (1.327)	17.029 (< 0.01) *
	Range	5.400 (1.798)	26.563 (11.025)	13.097 (< 0.01) *
Nonlinear	ApEn	1.706 (0.131)	1.331 (0.119)	-17.450 (< 0.01) *
	SaEn	1.800 (0.218)	1.166 (0.236)	-18.421 (< 0.01) *
	LyE	0.0135 (0.009)	0.0505 (0.014)	16.210 (< 0.01) *
	<i>Nonparametric</i>	Median (Range)	Median (Range)	Significance <i>Z</i> (<i>p</i>-value)
	RQA %REC	0.000179 (0.0013)	0.00186 (0.0103)	-4.625 (< 0.01) *

Table 3: Results of paired t-tests performed on variability measures for acceleration at the foot and trunk in the sagittal plane during walking in healthy controls; * significant difference between locations.

Sagittal Plane		Trunk Mean (St. Dev)	Foot Mean (St. Dev)	Significance <i>T statistic (p-value)</i>
Linear	RMS	1.669 (0.480)	6.620 (1.767)	20.217 (< 0.01) *
	Range	5.322 (0.211)	34.975 (14.265)	12.553 (< 0.01) *
Nonlinear	ApEn	1.677 (0.139)	1.111 (0.137)	-26.952 (< 0.01) *
	SaEn	1.733 (0.205)	1.153 (0.245)	-18.421 (< 0.01) *
	LyE	0.0125 (0.0059)	0.0449 (0.0104)	17.652 (< 0.01) *
	Nonparametric	Median (Range)	Median (Range)	Significance <i>Z (p-value)</i>
	RQA %REC	0.000323 (0.0019)	0.0161 (0.0956)	-5.086 (< 0.01) *

1. D. 2. Specific Aim #1: Hypothesis 2 (H1.2)

The second hypothesis of aim one is focused on determining if variability of accelerations in upper and lower segments during walking differs between healthy control subjects and persons with MS. A summary of these results can be found in Table 4 and Figure 7.

For RMS of accelerations in the frontal plane, a significant main effect for Location was found ($F_{1,71}: 485.022, p < 0.01$) where RMS at the foot was larger than RMS at the trunk. No

significant main effect was found for Group ($F_{1,71}$: 0.191, $p = 0.663$). No significant interaction was found for Location x Group ($F_{1,71}$: 1.244, $p = 0.268$).

For RMS of accelerations in the sagittal plane, a significant main effect for Location was found ($F_{1,71}$: 775.292, $p < 0.01$) where RMS at the foot was larger than RMS at the trunk. No significant main effect was found for Group ($F_{1,71}$: 0.099, $p = 0.754$). No significant interaction was found for Location x Group ($F_{1,71}$: 0.009, $p = 0.924$).

For range of accelerations in the frontal plane, a significant main effect for Location was found ($F_{1,72}$: 348.219, $p < 0.01$) where range at the foot was larger than range at the trunk. No significant main effect was found for Group ($F_{1,72}$: 0.524, $p = 0.472$). No significant interaction was found for Location x Group ($F_{1,72}$: 0.022, $p = 0.882$).

For range of accelerations in the sagittal plane, a significant main effect for Location was found ($F_{1,72}$: 459.938, $p < 0.01$) where range at the foot was larger than range at the trunk. No significant main effect was found for Group ($F_{1,72}$: 0.001, $p = 0.979$). No significant interaction was found for Location x Group ($F_{1,72}$: 0.073, $p = 0.787$).

For ApEn of accelerations in the frontal plane, a significant main effect for Location was found ($F_{1,70}$: 584.966, $p < 0.01$) where ApEn at the trunk was higher than ApEn at the foot. No significant main effect was found for Group ($F_{1,70}$: 0.091, $p = 0.764$). No significant interaction was found for Location x Group ($F_{1,70}$: 2.023, $p = 0.159$).

For ApEn of accelerations in the sagittal plane, a significant main effect for Location was found ($F_{1,70}$: 1703.745, $p < 0.01$) where ApEn at the trunk was higher than ApEn at the foot. No significant main effect was found for Group ($F_{1,70}$: 0.767, $p = 0.384$). No significant interaction was found for Location x Group ($F_{1,70}$: 0.018, $p = 0.894$).

For SaEn of accelerations in the frontal plane, a significant main effect for Location was found ($F_{1,76}$: 537.441, $p < 0.01$) where SaEn at the trunk was higher than SaEn at the foot. No significant main effect was found for Group ($F_{1,76}$: 0.044, $p = 0.835$). No significant interaction was found for Location x Group ($F_{1,76}$: 3.064, $p = 0.084$).

For SaEn of accelerations in the sagittal plane, a significant main effect for Location was found ($F_{1,75}$: 397.126, $p < 0.01$) where SaEn at the trunk was higher than SaEn at the foot. No significant main effect was found for Group ($F_{1,75}$: 0.305, $p = 0.583$). No significant interaction was found for Location x Group ($F_{1,75}$: 1.512, $p = 0.223$).

For LyE of accelerations in the frontal plane, a significant main effect for Location was found ($F_{1,68}$: 471.820, $p < 0.01$) where LyE at the foot was higher than LyE at the trunk. No significant main effect was found for Group ($F_{1,68}$: 3.836, $p = 0.054$). No significant interaction was found for Location x Group ($F_{1,68}$: 0.099, $p = 0.754$).

For LyE of accelerations in the sagittal plane, a significant main effect for Location was found ($F_{1,66}$: 364.566, $p < 0.01$) where LyE at the foot was higher than LyE at the trunk. No significant main effect was found for Group ($F_{1,66}$: 1.729, $p = 0.193$). A significant interaction was found for Location x Group ($F_{1,66}$: 35.152, $p < 0.01$). Post hoc tests revealed that at the trunk, LyE was significantly higher in PwMS ($t = -3.251$, $p < 0.01$) compared to HC. At the foot, LyE was significantly higher in HC ($t = 3.533$, $p < 0.01$) compared to PwMS.

A Wilcoxon signed-rank test showed that RQA %REC at the foot was higher than at the trunk in HC ($Z = -4.625$, $p < 0.01$) in the frontal plane. In PwMS, RQA %REC at the foot was higher than at the trunk ($Z = -4.564$, $p < 0.01$) in the frontal plane.

RQA %REC of accelerations at the foot in the frontal plane were significantly lower in HC (Mdn = 0.00186) compared to PwMS (Mdn = 0.0127), $U = 1090.00$, $p < 0.01$. RQA %REC

of accelerations at the trunk in the frontal plane were significantly lower in HC (Mdn = 0.000179) compared to PwMS (Mdn = 0.00186), $U = 1268.50$, $p < 0.01$.

A Wilcoxon signed-rank test showed that RQA %REC at the foot was higher than at the trunk in HC ($Z = -5.086$, $p < 0.01$) in the sagittal plane. In PwMS, RQA %REC at the foot was higher than at the trunk ($Z = -5.052$, $p < 0.01$) in the sagittal plane.

RQA %REC of accelerations at the foot in the sagittal plane were significantly higher in HC (Mdn = 0.0161) compared to PwMS (Mdn = 0.0109), $U = 411.00$, $p < 0.01$. RQA %REC of accelerations at the trunk in the sagittal plane were not significantly different between HC (Mdn = 0.000323) and PwMS (Mdn = 0.000520), $U = 796.00$, $p = 0.094$.

Table 4: Results of two-way ANOVA in frontal and sagittal plane to test for main effect of location (trunk, foot), main effect of group (HC, PwMS), and significant interaction (location x group). Values are reported as: F-ratio (p-value). * significance < 0.05.

	Frontal Plane			Sagittal Plane		
	Location	Group	Interaction	Location	Group	Interaction
RMS	486.022 (< 0.01)*	0.191 (= 0.663)	1.244 (= 0.268)	775.292 (< 0.01)*	0.099 (= 0.754)	0.009 (= 0.924)
Range	348.219 (< 0.01)*	0.524 (= 0.472)	0.022 (= 0.882)	459.938 (< 0.01)*	0.001 (= 0.979)	0.073 (= 0.787)
ApEn	584.066 (< 0.01)*	0.091 (= 0.764)	2.023 (= 0.159)	1703.745 (< 0.01)*	0.767 (= 0.384)	0.018 (= 0.894)
SaEn	537.441 (< 0.01)*	0.044 (= 0.835)	3.064 (= 0.084)	397.126 (< 0.01)*	0.305 (= 0.583)	1.512 (= 0.223)
LyE	471.820 (< 0.01)*	3.836 (= 0.054)	0.099 (= 0.754)	364.566 (< 0.01)*	1.729 (= 0.193)	35.152 (< 0.01)*

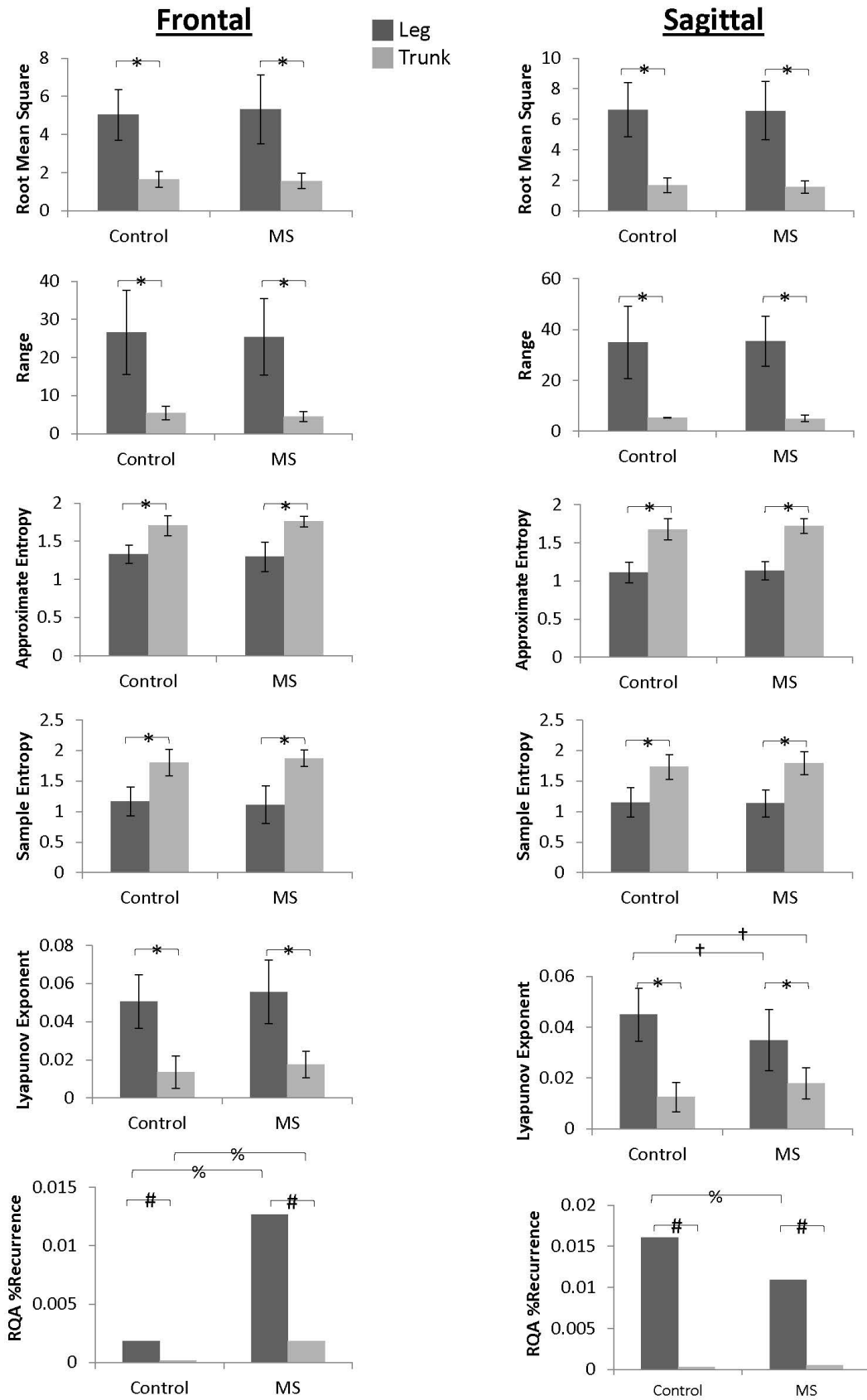


Figure 6: Variability measures for the frontal and sagittal planes.

Significant main effect for *Location ($p < 0.05$)

Significant main effect for 8Group ($p < 0.05$).

Significant interaction for Location x Group; †Post hoc test significant difference ($p < 0.05$).

Mann-Whitney U test significant difference; # ($p < 0.05$).

Wilcoxon signed rank test significant difference; % ($p < 0.05$).

1. E. Specific Aim #2

1. E. Specific Aim #2: Hypothesis 1 (H2.1)

The first hypothesis of specific aim 2 is focused on examining the relationships between variability of accelerations in upper and lower body segments during walking in healthy control subjects. In the frontal plane, HC subjects display significant positive correlations in all variability measures between the trunk and foot except for RQA %REC. In the sagittal plane, HC subjects display significant positive correlations in all variability measures except for Range and LyE. All correlations are presented in Table 3.

1. E. Specific Aim #2: Hypothesis 2 (H2.2)

The second hypothesis for aim two is focused on comparing intersegmental relationships between HC subjects and PwMS. In the frontal plane, ApEn and SaEn showed that higher regularity at the feet was correlated with higher regularity at the trunk in HC, but there was no significant correlation in PwMS. In the sagittal plane, larger range of acceleration at the feet was significantly correlated with larger range of acceleration at the trunk in PwMS, but there was no significant correlation in HC. In the sagittal plane, higher regularity (SaEn) at the feet was significantly correlated with higher regularity at the trunk in HC, but there was no significant correlation in PwMS. In the sagittal plane, more dynamic stability at the feet was correlated with more dynamic stability at the trunk in PwMS, but not in HC. In the sagittal plane, more recurrent patterns of accelerations at the feet were significantly correlated with more recurrence

at the trunk in HC, but there was no significant correlation in PwMS. Scatter plots illustrating the relationships between variability of acceleration at the trunk and at the feet can be found in the appendix.

Table 4. Correlations to measure relationship between trunk and foot acceleration variability in frontal and sagittal planes in healthy control subjects (HC) and persons with MS (PwMS); * significant correlation.

Plane		Variable	HC <i>R-value</i> (<i>p-value</i>)	PwMS <i>R-value</i> (<i>p-value</i>)
Frontal	Linear	RMS	0.565 (< 0.01) *	0.732 (< 0.01) *
		Range	0.711 (< 0.01) *	0.485 (< 0.01) *
	Nonlinear	ApEn	0.430 (< 0.01) *	0.252 (0.127)
		SaEn	0.541 (< 0.01) *	0.054 (= 0.740)
		LyE	0.334 (= 0.046) *	0.396 (= 0.020) *
		RQA %REC	0.294 (= 0.108)	0.284 (= 0.088)
Sagittal	Linear	RMS	0.810 (< 0.01) *	0.791 (< 0.01) *
		Range	0.274 (= 0.111)	0.372 (= 0.024) *
	Nonlinear	ApEn	0.550 (< 0.01) *	0.397 (= 0.015) *
		SaEn	0.510 (< 0.01) *	-0.098 (= 0.548)
		LyE	0.259 (= 0.145)	0.458 (< 0.01) *
		RQA %REC (Spearman's Correlations)	0.544 (< 0.01) *	0.310 (= 0.074)

Discussion – Chapter #5

1. F. Specific Aim #1

Specific Aim 1, Hypothesis 1

The goal of the first specific aim was to determine if variability of accelerations at the foot and at the trunk during walking differ between healthy control subjects and persons with MS through the use of wireless sensors. Specific aim 1, hypothesis one stated that healthy control subjects would display larger magnitudes of variability at the feet compared to the trunk and that the trunk would display more periodic patterns of variability compared to the foot.

Healthy control subjects demonstrated significantly larger magnitudes of variability at the feet compared to the trunk in the frontal and sagittal planes. These results are in agreement with findings published in previous studies evaluating how accelerations are attenuated from inferior to superior segments of the body [51]. During walking, the feet act to brake and subsequently propel the body forward, as well as catch the body from falling forward with each subsequent step. This high degree of movement relative to the rest of body accounts for the stark differences in the amount of variability between lower and upper body segments. Further, a possible reason for decreasing variability of acceleration from inferior to superior body segments is to keep the trunk, and therefore the body's center of mass, as stable as possible to minimize energy expenditure during walking [83, 84]. Additionally, it is important for the trunk to provide a stable base for the head, as the head houses the visual and vestibular systems which play a major role in the maintenance of balance and postural stability [13]. The present study shows that the feet display larger magnitudes of variability compared to the trunk during walking. This is important because the body must stabilize and reduce unwanted variability in center of mass motion during walking. Larger magnitudes of acceleration at the trunk will require the system to

work harder to arrest the center of mass momentum and redirect it from step to step, and will therefore be less efficient [16].

To better understand underlying patterns and possible mechanisms of inter-segmental control, nonlinear variability measures were also used in this study to assess the structure of the variability of accelerations at the foot and at the trunk during walking. Contrary to the original hypothesis, measures of entropy (ApEn, SaEn) revealed that healthy control subjects walked with significantly more regular patterns of accelerations (lower values of entropy) at the foot compared to the trunk in the frontal and in the sagittal plane. This result indicates a more regular pattern at the feet compared to the trunk, and signifies less variability of acceleration at the foot from step to step compared to the trunk. This finding suggests that the body aims to maintain a predictable foot motion during each step, resulting in a consistent base of support while walking. With regular motion of the feet during walking, the trunk may be free to adapt and react to postural disturbances to maintain stability. The adaptability of the trunk relative to the foot in the present study is represented by higher ApEn and SaEn of the trunk compared to the foot. Previous studies on stability during walking and quiet standing have illustrated that there is a level of movement variability which is healthy and demonstrates adaptability of the system [58, 59]. In contrast, without a predictable base of support, the trunk may have decreased adaptability, leading to fall risk. This conclusion is supported by previous studies which found that more variable foot motion is indicative of decreased whole body stability and likely increased fall risk [23, 32]. The results of the current study evaluate foot and trunk acceleration simultaneously and show that foot accelerations are relatively more regular compared to trunk accelerations during walking in HC.

The evaluation of dynamic stability (LyE) also provides important information about control of movement at the feet and at the trunk by measuring the rate of divergence or convergence between trajectories of the embedded time series in a phase space. In other words, LyE measures a systems ability to correct small perturbations, and ultimately can be used to infer the predictability of the system. Our results showed that accelerations at the foot displayed larger values of LyE compared to the trunk in the frontal and in the sagittal plane. A larger LyE is indicative of altered dynamic stability of the system. Therefore, our results show that the accelerations at the trunk display more dynamic stability compared to accelerations at the feet. It should be noted that LyE is a measure of dynamic stability in mathematical terms, and is not a direct measure of someone's functional stability during gait. Nevertheless, the LyE results provide important information about the possible mechanisms present to control foot and trunk motion. Specifically, more dynamically stable accelerations at the trunk may be indicative of the body prioritizing stability at the trunk, effectively stabilizing the center of mass and providing a stable support for the head. These results are in agreement with previous findings which used three dimensional motion capture to track upper and lower body motion during treadmill gait and found larger LyE values in inferior body segments compared to superior segments during walking [56]. In the current study, a similar testing paradigm was used but instead of data gathered by a motion capture system, wireless inertial sensors were employed to gather the data during walking. The agreement in these results offers support for the utility of these sensors in examining motion in upper and lower segments of the body.

Recurrence quantification analysis is a relatively new technique to be applied to biomechanical data, specifically gait analysis. Our results show that accelerations at the feet are more recurrent compared to accelerations at the trunk in the sagittal and frontal planes for HC

during walking. More recurrent patterns of acceleration at the feet indicate that the accelerations at the feet revisit similar areas of the state space more often than accelerations at the trunk. In other words, accelerations at the feet appear to be less random compared to accelerations at the trunk. This finding is in agreement with the trends shown in our entropy results as patterns of accelerations at the feet were found to be more regular, and therefore less random, than accelerations at the trunk. When taken together these results show that while there are lower magnitudes of acceleration variability at the trunk compared to the foot, the accelerations at the feet are more regular and more periodic than accelerations at the trunk.

Specific Aim 1, Hypothesis 2

We hypothesized that PwMS would exhibit less variability of foot and trunk accelerations during walking compared to healthy control subjects. No significant differences were found between groups for the magnitude of variability (RMS, Range) in the frontal or sagittal plane. In the frontal and sagittal planes PwMS and HC elicited greater magnitudes of variability at the foot compared to the trunk. These results again agree with previous findings that accelerations are attenuated from inferior segments to superior segments of the body during walking [51]. The current study shows that these accelerations are attenuated from inferior to superior segments of the body in HC and also in PwMS. It is possible that progression of MS may eventually diminish one's ability to attenuate accelerations during walking in this manner, as previous studies have shown that attenuation strategies may be altered in aging population such that they are unable to attenuate accelerations from lower to upper segments during walking [85]. However, it is clear that within our subject groups, no significant differences were identified between groups by measures of variability magnitude (RMS and range).

Measures of entropy also showed no differences in results between PwMS and HC in the sagittal and frontal planes. HC subjects and PwMS both showed significantly lower values of entropy at the foot and at the trunk in the sagittal and frontal planes. These results signify that accelerations at the feet are more regular than accelerations at the trunk in HC and PwMS. Previous studies have found that PwMS display altered variability patterns compared to HC [10, 17, 86]. It is possible that similar differences were not identified in the current study due to the subjects in the MS group being able to walk with similar function to HC as shown by the similar preferred gait speed. It is also possible that the amount of potential variability was decreased by enforcing a constant gait speed while walking on the treadmill. However, previous studies have shown this to not necessarily be a significant constraint, as treadmill gait was shown to be similar to overground gait [87].

In the frontal plane, there were no significant differences in dynamic stability between HC and PwMS. Both groups showed larger values of LyE at the foot compared to the trunk in the frontal and sagittal plane, effectively showing that both HC and PwMS display more predictable accelerations at the trunk compared to the feet. However, in the sagittal plane, group differences were found as LyE of accelerations at the feet was higher in HC compared to PwMS. Additionally LyE of accelerations at the trunk was lower in HC compared to PwMS in the sagittal plane. Therefore, our results show that PwMS display greater predictability of foot accelerations in the sagittal plane compared to HC. The sagittal plane is the primary plane of motion during walking, as the legs swing and propel the forward with each step. Step length may be controlled via relatively passive mechanisms compared to step width which is considered to be maintained from step to step [88]. One possible reason for this difference between groups is that PwMS constrain their step length in order to reduce variability from step to step, which

requires constant feedback from the sensorimotor system [18]. Compared to HC, PwMS may display a more constrained walking system for a variety of reasons including both physiological and psychological reasons. PwMS have been shown to display delayed sensorimotor responses, and this may cause a slower response time to any perturbations encountered during walking which may effectively lead to risk of falls [6]. To combat this danger to falls, it is possible that PwMS develop a more tightly controlled gait pattern at the feet in an effort to reduce variability due to small perturbations during walking. At the trunk, healthy controls exhibited significantly lower LyE compared to PwMS, showing that accelerations at the trunk are less dynamically stable for PwMS compared to HC. This finding is in agreement with previous which have shown that aging populations, populations with a known neuromuscular disorder, populations of fall-prone individuals, and specifically PwMS all display higher LyE at the trunk compared to healthy control subjects [10, 22, 23, 89]. In reference to the group differences found at the foot, it is possible that the decrease in dynamic stability at the trunk is partially due to the added constraint at the feet. However, it is also possible that the decrease in dynamic stability at the trunk creates an additional weight on the system which requires the foot motion to be constrained to maintain total body stability.

There were significantly different results between groups for RQA %REC in the frontal and sagittal planes. In the frontal plane, accelerations at the foot were more recurrent compared to accelerations at the trunk in HC and PwMS. Additionally, PwMS exhibited significantly higher recurrence at the trunk and at the feet compared to HC. Therefore, it appears that in the frontal plane, PwMS exhibit significantly less random accelerations at the feet and at the trunk compared to HC. However, PwMS also showed less recurrence at the foot in the sagittal plane compared to HC. Recalling that previous studies have found that motion in the sagittal plane

seems to be controlled by passive mechanisms, while motion in the frontal plane seems to be controlled by more active feedback mechanisms, our results in fact seem to support this concept [26]. If sagittal plane motion is considered to be more passive in nature, then it should also require less active maintenance from step to step in a healthy individual, and therefore accelerations at the foot should revisit similar patterns during gait. Our results illustrate this by finding more recurrent patterns of acceleration at the foot in the sagittal plane for HC compared to PwMS. The ability of the system to passively control sagittal plane motion may be affected in PwMS and the accelerations patterns are therefore less likely to repeat themselves. Similarly, if the frontal plane is considered to be controlled by more active mechanisms, one would expect to possibly find more complexity in HC, identified as less repetitive patterns of accelerations during walking. In the frontal plane, the higher rate of recurring patterns for accelerations at the foot and trunk in PwMS may therefore be indicative of the system adding constraints to the gait cycle in order to maintain more repetitive patterns at the foot and at the trunk.

Specific Aim 2, Hypothesis 1

We hypothesized that a relationship would exist between variability of accelerations at the feet and variability of accelerations at the trunk during walking in healthy control subjects. Our results show a positive correlation between RMS at the foot and the trunk in the sagittal and frontal plane in HC. Accelerations at the feet are transferred to the upper body through the physical connections of the legs, pelvis, and trunk. The physical link between these segments gives rise to a strong relationship between magnitudes of variability at the feet and at the trunk in both the sagittal and frontal planes. As the sagittal plane is the primary plane of motion during gait (flexion/extension of the lower limb joints), motion at the feet will certainly influence the motion at the trunk. In the sagittal plane, a deviation from the normal pattern at the feet (i.e. a

change in step length) should similarly be reflected by a deviation from the normal pattern at the trunk.

In HC, range of accelerations at the feet was significantly correlated with range of accelerations at the trunk in the frontal plane, but there was no significant correlation in the sagittal plane. Recalling that subjects display much larger ranges of accelerations at the feet compared to the trunk, a possible explanation for this finding is that HC subjects are able to maintain a very small range of accelerations at the trunk regardless of how large the range of accelerations are at the feet in the sagittal plane. In the frontal plane, range of accelerations may be more closely tied as maintenance of frontal plane stability may require more active mechanisms of control such as a deviation of the trunk to one side requiring the subsequent step to deviate to that same side to arrest and return the center of motion to the normal trajectory [16, 32].

Measures of entropy in HC revealed significant relationships between foot and trunk acceleration regularity in the frontal and in the sagittal plane. Specifically, as accelerations at the foot are more regular, accelerations at the trunk are also more regular. A possible explanation for this finding may be in the fact that motion at the foot drives forward propulsion during gait, and will therefore be highly influential trunk motion. A more regular pattern of accelerations at the feet is indicative of more regular foot placement from step to step, which provides a reliable base of support during gait. With a reliable base of support from step to step, the trunk also can follow a more regular pattern of motion. However, it is important to recall that motion at the trunk was less regular (higher ApEn) compared to motion at the feet.

In the frontal plane, LyE values showed a significant relationship between foot and trunk accelerations for HC. Effectively, this result shows that more predictable motion at the trunk is

related to more predictable motion at the feet in the frontal plane for HC. During walking, step width is altered from step to step in the frontal plane to maintain a sufficient base of support and control mediolateral motion of the center of mass. This may explain the significant relationship between accelerations at the feet and accelerations at the trunk in the frontal plane as a more predictable base of support allows for more predictable motion of the center of mass during walking. However, LyE values for accelerations at the foot and at the trunk did not show a significant relationship in the sagittal plane. Noting that dynamic stability was lower at the feet (higher LyE) compared to the trunk, the lack of significant relationship in the sagittal plane may be illustrating that the trunk is able to maintain stability regardless of how predictable accelerations are at the feet in the sagittal plane.

RQA %REC of accelerations at the foot and at the trunk were significantly related to each other in the sagittal plane but not in the frontal plane for HC. The lack of correlations in the frontal plane may indicate that control of trunk motion aims to decrease variability magnitude at the trunk but may not be related to increasing the predictability of variability at the trunk in the frontal plane. This explanation is tied with our findings that acceleration variability showed more recurring patterns at the foot compared to the trunk in the frontal plane. In the sagittal plane, more recurrence for accelerations at the foot was related to more recurrence for accelerations at the trunk in HC. Due to the physical connection between foot and trunk motion during walking, and noting that the sagittal plane is the primary plane of motion during gait, it appears that more recurrent patterns at the trunk are closely tied to more recurrent patterns at the foot, as the foot will provide a predictable base of support for the trunk.

Specific Aim 2, Hypothesis 2

We hypothesized that the strength of relationships would differ between variability of accelerations at the feet and variability of accelerations at the trunk during walking in PwMS compared to healthy control subjects. RMS results displayed significant positive correlations in the frontal and sagittal planes for both HC and PwMS. Although significant correlations were found in the sagittal and frontal planes for HC and PwMS, the differences in the strength of frontal plane correlations in HC and PwMS are of particular interest. Specifically, the relationship between RMS of accelerations at the feet and at the trunk in the frontal plane was much stronger in PwMS compared to HC. This may indicate that mechanisms which attenuate accelerations from inferior to superior segments may not be as active or may be altered in PwMS. These mechanisms typically include passive and active components, the active components being spinal musculature which may have slowed neuromuscular responses due to the physiological effects of MS [5, 7]. Motion at the foot is mechanically linked to motion at the trunk, and therefore larger magnitudes of acceleration variability at the foot will likely be related to larger magnitudes of acceleration variability at the trunk in both the frontal and sagittal planes in HC and in PwMS. Although underlying control mechanisms and structure of variability may be different between groups, the physical link between motion at the feet and motion at the trunk still exists in PwMS as it does in HC.

In the sagittal plane, there was a significant relationship between range of accelerations at the feet and range of accelerations at the trunk in PwMS, but not in HC. The lack of correlation for range of acceleration in the frontal plane for HC may represent differences in the groups' segmental control strategies and ability to attenuate accelerations from inferior to superior segments of the body during walking. Attenuation of these accelerations is thought to be carried via absorption and damping within spinal structures and activation of spinal musculature [5, 13].

The mechanisms which govern the attenuation of ascending accelerations may be slightly weakened in PwMS, as suggested by a significant correlation indicating that larger range of accelerations at the feet are related to larger range of accelerations at the trunk in the sagittal plane. As muscle activation is commonly affected in MS, it is possible this could play a role in the relationship between acceleration ranges in the sagittal plane. Specifically, a decreased ability to adequately activate skeletal musculature of the spine may cause the trunk to absorb more accelerations via passive mechanisms, which are considered to typically only address higher frequency accelerations [5]. If this is the source of the difference in range relationships between HC and PwMS, it makes sense as to why this difference appears only in the sagittal plane, as large magnitude low frequency accelerations tend to dominate movement in the sagittal plane [5].

Measures of entropy also revealed differences in the relationship between accelerations at the feet and at the trunk in HC and PwMS. Results showed that in PwMS, there were no significant relationships for SaEn of accelerations at the feet and at the trunk in the frontal or sagittal plane. ApEn showed a significant, though relatively weak relationship between entropy of accelerations at the feet and at the trunk in the sagittal plane for PwMS. The difference between the two groups identifies that more regular patterns of acceleration at the feet are related to more regular patterns of acceleration at the trunk in HC, but not in PwMS. Assuming the healthy control subjects display healthy patterns of variability during walking, the results suggest that MS affects the relationship between the regularity of acceleration at the feet and the trunk during walking. The results from the current study show that accelerations at the foot were more regular compared to accelerations at the trunk in both groups and both planes. Sagittal plane results from the current study also show that foot motion was more predictable (lower LyE) in

PwMS compared to HC, while trunk accelerations were less predictable and displayed less complexity (higher LyE) in PwMS compared to HC. Our findings support conclusions made by previous studies which have also found that accelerations at the trunk display higher LyE in PwMS compared to HC, concluding that PwMS display lower complexity in trunk acceleration variability which indicates a less healthy or adaptable system [10, 59]. In combination, these results may indicate that PwMS may have difficulty stabilizing their trunk segment during walking, as increased regularity in at the feet does not correlate with increased regularity at the trunk and sagittal plane motion at the trunk was found to be less predictable in PwMS compared to HC. It is possible the observed altered variability in PwMS may be due to the neuropathology of MS which affects the connectivity of the neural systems and may be the cause of decreased complexity and adaptability of the system [86]. It may therefore be desirable to investigate the structure of variability in populations with a neurological disorder in order to better understand how the sensorimotor system is altered.

Our results showed that in the frontal plane, increased LyE for foot accelerations was significantly correlated with increased LyE for trunk accelerations during walking in HC and PwMS. This finding indicates that more dynamically stable motion at the feet is related to more dynamically stable motion at the trunk in the sagittal plane for both HC and PwMS. However, in the sagittal plane, a significant relationship between LyE of accelerations at the feet and at the trunk was found in PwMS but not in HC. This finding indicates that an increase in dynamic stability of the trunk may be related to an increase in dynamic stability of the feet in PwMS but not in HC in the sagittal plane. This finding provides insight into the mechanisms that may be affected in PwMS. Our study found that PwMS elicit more dynamic stability of the feet in the frontal plane during walking compared to HC, but less dynamic stability in the sagittal plane. In

combination, these findings may indicate that PwMS are unable stabilize their trunk during walking independent of foot motion in the sagittal plane. Dynamic stability provides information on the mathematical stability of the system, and identifies complexity within the time series which is considered to be characteristic of underlying processes governing the time series. PwMS have been shown to display higher LyE of the lower and upper trunk during walking compared to HC [10, 56]. However, the results of the current study demonstrate altered relationships between upper and lower segmental motion in PwMS compared to HC. Coupled with the results of the current study, it is possible that LyE is able to quantify differences in underlying sensorimotor control mechanisms that are affected in PwMS at upper and lower body segments. Altered dynamic stability in PwMS at upper and lower body segments may indicate that LyE measuring a part of the system related to control mechanisms which govern whole body stability.

RQA %REC displayed no significant correlations between recurrence of acceleration at the foot and at the trunk for HC or PwMS in the frontal plane. These results show that more recurrent patterns at the feet do not relate to more recurrent patterns at the trunk in the frontal plane. This may illustrate that the system aims to decrease variability of accelerations at the trunk in the frontal plane, though not necessarily by increasing the recurrence of patterns at the trunk. This conclusion relates to our findings that showed that recurrence of accelerations were much higher at the feet compared to the trunk in the frontal plane. Increased recurrence of acceleration patterns at the feet was significantly related to increased recurrence of acceleration patterns at the trunk in the sagittal plane for HC but not for PwMS. This may be indicative of an increase in active control of motion in the sagittal plane in PwMS, as the system works to constrain motion and effectively reduce variability of the trunk during walking. Previous studies

have shown that persons with altered sensorimotor systems show less recurrent patterns of movement during walking, indicative of the importance of the sensorimotor system in maintaining stable gait [90]. Although RQA has not been used in PwMS, the findings of the current study coupled with known sensorimotor deficits inherent to MS support the conclusions of previous studies [8, 18, 90].

1. G. Limitations

A limitation of this study is that the data was collected on a motorized treadmill, which may have added a constraint to the subjects' gait by holding a constant speed and confining them to walk within the boundaries of the treadmill belt. While the treadmill could have eliminated some variability in the subjects' gait, the use of the method was necessary to record a time series of sufficient length and the use of treadmill gait to assess variability of movement patterns is well established [17, 91-93]. Previous studies have also supported the validity of gait analysis using a treadmill, showing that treadmill gait is similar to overground walking [87]. Additionally, other outcome measures could have also been included to identify further differences between HC and PwMS. However, the metrics used in the current study were chosen specifically to quantify the magnitude (linear measures) and structure (nonlinear measures) of variability. Further, these variability measures were selected to compliment each other, and additional measures would have either been redundant or inappropriate for use in the analysis.

Limitations in sensor location were also present in the current study. Only the right leg was evaluated for all measures, which may have had effects on the results if any person exhibited significantly asymmetric patterns of motion at the feet. The single leg evaluation was chosen with the assumption that a significant deviation in patterns did not exist between the right and

left foot of any subject. In other words, while asymmetric gait parameters may exist, the variability of the single foot was assumed to be representative of the variability at both feet. Similarly, only one sensor was used to evaluate motion of the trunk. As previous studies have shown that accelerations are attenuated from inferior to superior portions of the trunk, the single sensor at the sternum was chosen in regards to a primary aim of the current study. Specifically, to examine differences between accelerations at the feet compared to the trunk the sensor located over the sternum was chosen in order to maximize the amount of attenuation to the acceleration prior to being recorded by the sensor, therefore the theoretically largest differences in accelerations between the foot and trunk were measured. Future studies could address these limitations by repeating the analysis for both feet, and including measurements taken from a sensor located in the lumbar area of the trunk.

Conclusions – Chapter #6

The use of linear and nonlinear variability measures in the current study revealed differences between upper and lower segment control during walking in HC and PwMS. Magnitudes of acceleration variability were higher at the foot compared to the trunk in HC and PwMS. However, accelerations at the feet tended to be more regular and recurrent but less dynamically stable compared to accelerations at the trunk in HC and PwMS. The information identified by nonlinear variability measures demonstrate their utility in understanding control of motion in healthy individuals as well as individuals with a known sensorimotor disorder, as variability was shown to be altered in PwMS. Additionally, examining relationships between upper and lower segment motion during walking provided useful information in regards to whole body control, and how this control is affected in persons with a sensorimotor deficit. Persons with known sensorimotor deficits have been shown to have altered variability during standing compared to healthy controls as well as other neurological pathologies, and further studies of gait stability which include other neurological disorders may help in understanding how variability can provide information about the sensorimotor system [86].

The ability for the trunk to control and attenuate motion during walking is critical to providing a stable base for the head which houses various mechanisms which govern balance control [13]. The results of the current study lend support to the development of a “gait stability index” which demonstrates the relationship between upper and lower body segments during walking. Such a gait stability index could be measured via wireless sensors and would ideally take into account upper and lower body metrics to provide an objective measure of a person’s whole body stability during walking. The gait index could then be used by clinicians as a biomarker of a patient’s functional mobility status or fall risk, and could be included as a metric

to be checked regularly to monitor longitudinal changes to a person's stability and fall risk. Measures of nonlinear variability may be able to help identify underlying mechanisms affected by specific neuromuscular disorders, and may allow therapists the ability to target certain deficiencies in the system. Future studies should aim to expand this research to populations with other neuromuscular pathologies which could further identify how coordination between foot and trunk motion during walking is affected by altered dynamic systems. Additionally, future studies should aim to apply this analysis to overground walking, in order to identify the relationships between upper and lower segment coordination in a more familiar and less constraining environment compared to treadmill gait. It would be of interest to examine healthy control subjects during overground walking when the environment is altered either via altered visual or sensory feedback, or by altering gait speed and examining how gait stability is specifically changed in response to these situations.

Appendix

Recruitment documents:



UNIVERSITY OF KANSAS MEDICAL CENTER
HUMAN SUBJECTS COMMITTEE

REQUEST TO ADD OR REVISE RECRUITMENT/RETENTION MATERIALS

RECEIVED
MAY 8 2013
HSC KUMC

STUDY INFORMATION

HSC #: 13495		
STUDY TITLE: Identification of Gait and Posture Deficits in Patients with Multiple Sclerosis		
PROTOCOL AMENDMENT NUMBER AND DATE (IF APPLICABLE):		
Principal Investigator: Jessie Huisinga		
DEPARTMENT: Landon Center on Aging		
E-mail: jhuisinga@kumc.edu	Phone: 913-945-7465	Mail Stop: 1005
Contact Person (if different than PI):		
E-mail:	Phone:	Mail Stop:

PROPOSED REVISIONS

This amendment contains (check all that apply):

ADVERTISEMENT AND RECRUITMENT MATERIALS

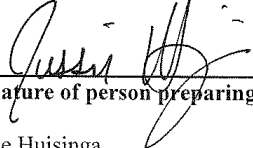
- ☒ Change/addition of advertisements including fliers, posters, brochures, newspaper ads, radio announcements, etc. *(Be sure to include a letter of permission from any non-KUMC locations at which you plan to post or distribute recruitment materials.)*

How will this advertisement be disseminated? (i.e., posted on a bulletin board, e-mailed, distributed at a clinic, broadcast on radio or television, etc.)

e-mailed to KUMC Faculty/Staff

PARTICIPANT EDUCATION AND RETENTION MATERIALS

- ☐ Change/addition of retention materials including newsletters, patient brochures, tokens of appreciation, diary cards, appointment reminders, etc.

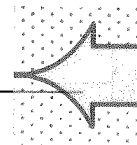


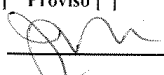

Signature of person preparing this document

Jessie Huisinga
Typed or Printed Name

5-7-13

Date



Human Subjects Committee Office Use Only	
HSC REVIEW: Approved <input checked="" type="checkbox"/> Proviso <input type="checkbox"/>	
HSC reviewer signature/date:	 5/22/13
HIPAA REVIEW: Approved <input type="checkbox"/> Proviso <input type="checkbox"/>	
HIPAA reviewer signature/date:	 5/23/13

Volunteers are needed to serve as healthy controls subjects in a study examining walking and balance in persons with multiple sclerosis. Male and female volunteers between the ages of 20 and 60 years of age are needed. Volunteers should be free from any lower extremity orthopedic problem such as arthritis or ligament/tendon injuries (i.e. ACL injuries or meniscus tears) and free from any neurological or vestibular problems. This is a one-visit study that will last approximately 2-3 hours and you will be compensated for your time. We will measure your walking and balance using a three dimensional motion capture system. There is no invasive testing involved, i.e. no blood draws or similar tests. To see if you qualify for this study, contact Sara Kurtz at skurtz@kumc.edu. In your inquiry, please indicate your age and sex.

PI for this study is Jessie Huisinga, PhD
HSC approval number 13495

Subject Name (First, Last):
Sex:
Ethnicity:

Address:

Phone Number:
Email:

1. What is your age?

2. When were you diagnosed with MS?

3. Are you currently taking Ampyra or Dalfampridine?

☐

Yes*

☐

No

4. Have you had any recent symptom exacerbations? If yes, then when approximately?

5. Do you feel like you have walking and balancing problems?

☐

Yes

☐

No

6. Do you wear an orthotic inside or outside? AFO?

- a. How often do you use the AFO and can you walk without it?

☐

I can walk without it.

☐

I cannot walk without it.*

- b. Do you walk with a cane/walker always or only in public?

☐

Always

☐

Only in public

- c. Can you walk 25 feet without any kind of support?

☐

Yes

☐

No*

7. Do you have any sort of orthopedic problem? Arthritis, joint replacements or pins in the body?

8. Do you have any vestibular problems? Any inner ear or balance disorders?

☐

Yes*

☐

No

9. Are you diabetic?

☐ Yes*

☐ No

*Circle one: Type I Type II

*Have you ever been diagnosed with diabetic neuropathy?

☐ Yes*

☐ No

10. Are you color blind?

☐ Yes

☐ No

11. Do you have any significant vision problems?

☐ Yes

☐ No

Screening tools specific to persons with Multiple Sclerosis:

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME _____

PERSONAL INFORMATION

Patient										
Date of Birth (04-Jun-1980)										
Centre Nr/Country										
Name of EDSS rater										
Date of Examination							2	0		

SYNOPSIS OF FS SCORES

1. Visual ¹		5. Sensory	
2. Brainstem		6. Bowel/Bladder ¹	
3. Pyramidal		7. Cerebral	
4. Cerebellar		¹ = converted FS Score	

EDSS Step

Signature

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		

Scotoma		
* Disc pallor		
FUNCTIONAL SYSTEM SCORE		→

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION	
Extraocular movements (EOM) impairment	
Nystagmus	
Trigeminal damage	
Facial weakness	

Hearing loss	
Dysarthria	
Dysphagia	
Other cranial nerve functions	
FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	> <	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			
LIMB STRENGTH	R	L	
Deltoids			
Biceps			
Triceps			
Wrist/finger flexors			
Wrist/finger extensors			
Hip flexors			

Knee flexors		
Knee extensors		
Plantar flexion (feet/toes)		
Dorsiflexion (feet/toes)		
* Position test UE, pronation		
* Position test UE, downward drift		
* Position test LE, sinking		
Able to lift only one leg at a time (grade in °)		
* Walking on heels		
* Walking on toes		
* Hopping on one foot		
SPASTICITY		
Arms		
Legs		
Gait		
FUNCTIONAL SYSTEM SCORE		

* = optional

¹ = converted FS Score

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION

Head tremor	
Truncal ataxia	
	R L
Tremor/dysmetria UE	
Tremor/dysmetria LE	

Rapid alternating movements UE impairment	
Rapid alternating movements LE impairment	
Tandem walking	
Gait ataxia	
Romberg test	
Other, e. g. rebound	
FUNCTIONAL SYSTEM SCORE	

5. SENSORY FUNCTIONS

SENSORY EXAMINATION

	R L
Superficial sensation UE	
Superficial sensation trunk	
Superficial sensation LE	
Vibration sense UE	
Vibration sense LE	

Position sense UE	
Position sense LE	
* Lhermitte's sign	
* Paraesthesiae UE	
* Paraesthesiae trunk	
* Paraesthesiae LE	
FUNCTIONAL SYSTEM SCORE	

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention	
Urinary urgency/incontinence	
Bladder catheterisation	

Bowel dysfunction	
* Sexual dysfunction	
FUNCTIONAL SYSTEM SCORE	

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION

+ Depression	
+ Euphoria	

Decrease in mentation	
* Fatigue	
FUNCTIONAL SYSTEM SCORE	

8. AMBULATION

Walking range as reported (without help or sticks)

meters	
in min	

Distance able to walk without rest or assistance	
≥ 100 meters, but < 200 meters	
≥ 200 meters, but < 300 meters	
≥ 300 meters, but < 500 meters	
≥ 500 meters but not unrestricted	
Unrestricted	
Actual distance (obligatory up to 500 m if possible)	
meters	

Requires constant assistance to walk 100 meters	
Unilateral assistance (in meters)	
Cane/crutch	
Other	
Bilateral assistance (in meters)	
Canes/crutches	
Other	
Assistance by another person (in meters)	

* = optional

¹ = converted FS Score

* Because depression, euphoria and fatigue are difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale

Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52

©2009 Ludwig Kappos, MD, Professor and Chair, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 09/08

Hauser Ambulation Index

- ☐ 0 = Asymptomatic; fully active.
- ☐ 1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.
- ☐ 2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.
- ☐ 3 = Walks independently; able to walk 25 feet in 20 seconds or less.
- ☐ 4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.
- ☐ 5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; or requires unilateral support but needs more than 20 seconds to walk 25 feet.
- ☐ 6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair* on occasion.
- ☐ 7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair* for most activities.
- ☐ 8 = Restricted to wheelchair; able to transfer self independently.
- ☐ 9 = Restricted to wheelchair; unable to transfer self independently.

*The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

Source: Hauser SL, Dawson DM, Leirich JR, Beal MF, Kevy SV, Propper RD, Mills JA, Weiner HL. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med. 1983 Jan 27;308(4):173-80.

Disease Steps

METHODS: For Disease Steps, classification of a patient is determined by history and neurologic examination as well as course of MS. The scale consists of the following categories:

- ☐ **0 = Normal:** functionally normal with no limitations on activity or lifestyle. Patients may have minor abnormality on examination, such as nystagmus or an extensor plantar. The course is relapsing-remitting with a return to baseline with or without treatment. These patients are not treated with any ongoing symptomatic therapy for MS.
- ☐ **1 = Mild disability:** mild symptoms or signs. These patients have mild but definite findings such as sensory abnormalities, mild bladder impairment, minor incoordination, weakness, or fatigue. There is no visible abnormality of gait. The pattern of disease is relapsing-remitting, but patients may not have a full return to baseline following attacks. These patients may use ongoing symptomatic therapy such as amantadine, baclofen, or oxybutynin.
- ☐ **2 = Moderate disability:** the main feature is a visibly abnormal gait, but patients do not require ambulation aids. The pattern of disease is relapsing-remitting or progressive.
- ☐ **3 = Early cane:** intermittent use of cane (or other forms of unilateral support including splint, brace, or crutch). These patients use unilateral support primarily for longer distances, but are able to walk at least 25 feet without it. The pattern of disease is relapsing-remitting or progressive.
- ☐ **4 = Late cane:** these patients are dependent on a cane or other forms of unilateral support and cannot walk 25 feet without such support (eg, these patients may hang on to furniture inside their homes or touch the wall when walking in clinic). Patients may use a scooter for greater distances (eg, malls). The pattern of disease is relapsing remitting or progressive.
- ☐ **5 = Bilateral support:** patients require bilateral support to walk 25 feet (eg, two canes or two crutches or a walker). They may use a scooter for greater distances. The pattern of disease is relapsing-remitting or progressive.
- ☐ **6 = Confined to wheelchair:** patients are essentially confined to a wheelchair or scooter. They may be able to take a few steps but are unable to ambulate 25 feet, even with bilateral support. They may show further progression including worsening hand function or inability to transfer independently.
- ☐ **U = Unclassifiable:** this category is used for patients who do not fit the above classification (eg, significant cognitive or visual impairment, overwhelming fatigue, or significant bowel or bladder impairment in an otherwise minimally impaired patient).

Source: Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler.* 1999 Oct;5(5):349-54.

Appendix Table 1: Root Mean Square results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	6.76	7.97	2.09	2.05
2	6.95	9.07	1.68	1.75
3	3.53	5.21	1.59	1.46
4	4.95	7.23	1.70	1.65
5	3.84	5.64	1.66	1.61
6	5.21	7.49	2.05	2.04
7	10.17	11.62	3.60	4.25
8	4.20	6.35	1.36	1.46
9	2.90	3.99	0.88	0.89
10	3.19	4.05	1.28	1.12
11	5.39	6.84	1.90	1.99
12	5.07	7.08	1.67	1.81
13	3.82	5.79	1.80	1.96
14	4.16	5.66	1.42	1.51
15	5.69	7.19	1.48	1.40
16	5.11	6.83	1.62	1.78
17	6.05	5.20	1.41	1.46
18	3.74	5.27	1.30	1.28
19	3.34	4.61	1.04	0.99
20	3.03	4.21	1.11	0.97
21	10.36	15.73	5.95	6.11
22	7.24	9.60	3.13	3.39
23	4.89	5.15	1.38	1.41
24	5.35	8.47	2.17	2.29
25	4.59	7.00	1.27	1.23
26	9.24	10.30	3.41	3.54
27	6.07	7.57	1.47	1.50
28	3.33	5.12	1.46	1.10
29	5.64	5.58	1.81	1.85
30	6.63	10.66	2.55	2.72
31	7.66	8.66	1.30	1.46
32	6.00	7.35	3.30	3.40
33	7.13	8.90	1.87	2.06
34	3.80	5.60	1.71	1.64
35	5.50	5.14	1.42	1.40
36	5.72	5.87	1.72	1.80
37	8.33	9.77	3.05	3.27
38	6.09	8.55	2.32	2.52

39	10.38	15.23	3.90	3.92
40	6.78	10.53	2.83	2.89

Appendix Table 2: Root Mean Square results for persons with MS.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	5.74	6.58	1.19	1.79
2	6.10	8.80	1.71	1.92
3	5.17	8.17	1.26	1.38
4	2.58	4.12	0.86	0.93
5	5.09	6.39	1.65	1.36
6	3.10	5.40	1.33	1.09
7	6.26	7.82	1.72	1.76
8	5.36	6.52	1.78	1.83
9	3.73	4.37	1.01	0.89
10	4.46	5.33	1.28	1.06
11	4.74	4.51	1.02	1.07
12	2.87	4.53	1.03	1.10
13	1.80	3.20	1.35	0.70
14	6.61	7.06	1.73	1.80
15	2.96	4.54	1.14	1.31
16	6.74	8.99	1.84	1.88
17	3.48	4.46	1.16	1.24
18	2.77	3.93	1.14	1.09
19	6.79	6.89	1.64	1.58
20	5.77	7.86	1.76	2.04
21	4.55	2.74	0.91	1.20
22	5.30	8.46	1.77	1.53
23	6.58	8.42	2.09	2.07
24	5.85	6.75	1.67	1.55
25	4.05	5.93	1.37	1.63
26	3.24	4.87	1.46	1.55
27	9.11	5.73	1.92	2.01
28	4.68	6.93	1.34	1.31
29	9.28	8.38	1.76	1.86
30	6.48	9.87	2.08	2.09
31	4.61	7.50	1.83	1.79
32	5.92	6.45	2.02	2.04

33	7.39	7.07	1.74	1.36
34	9.00	5.59	2.12	1.78
35	4.19	6.61	0.98	1.35
36	4.28	6.49	1.53	1.46
37	6.40	9.38	2.25	2.08
38	7.88	8.62	2.22	2.27
39	6.61	11.14	2.36	2.33
40	4.97	5.85	1.51	1.69

Appendix Table 3: Range results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	23.94	35.73	5.79	5.75
2	37.30	69.63	4.32	4.60
3	26.65	68.51	5.61	5.83
4	20.93	29.33	4.17	4.50
5	13.51	20.73	4.61	4.79
6	26.78	39.47	5.50	5.88
7	50.52	59.24	8.54	11.28
8	16.51	35.61	4.21	4.65
9	10.70	18.40	2.61	2.69
10	11.28	21.93	3.48	3.75
11	22.85	24.21	4.83	6.00
12	32.09	31.97	4.72	5.47
13	22.30	45.95	5.67	6.08
14	15.43	22.37	10.95	5.81
15	33.58	29.25	5.54	5.91
16	19.39	31.81	3.98	5.89
17	37.65	21.02	5.26	6.76
18	13.53	27.95	4.10	4.62
19	19.27	36.15	3.06	3.11
20	23.34	22.51	3.95	4.02
21	67.83	64.04	15.10	22.51
22	31.41	42.90	7.70	7.85
23	42.66	50.23	4.20	5.23
24	16.63	33.16	5.97	6.53
25	18.74	36.50	3.73	3.50
26	54.83	54.06	10.09	16.52

27	23.04	32.23	7.53	6.00
28	15.55	23.71	3.55	4.12
29	18.86	26.80	3.64	3.69
30	31.21	52.97	6.39	6.31
31	74.56	71.36	3.82	5.94
32	21.01	26.04	7.75	7.98
33	31.31	38.37	5.97	6.55
34	14.18	28.30	4.47	4.58
35	24.52	19.06	4.26	4.11
36	24.82	20.91	4.49	5.15
37	42.71	46.92	7.96	14.12
38	33.80	36.58	5.91	6.14
39	46.04	73.46	9.46	9.79
40	29.39	52.45	6.78	6.47

Appendix Table 4: Range results for persons with MS.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	25.62	25.15	4.00	10.46
2	18.35	37.34	3.63	4.48
3	26.90	46.77	3.67	5.06
4	16.74	41.44	3.48	3.68
5	23.52	27.66	4.60	4.64
6	18.31	37.35	4.27	5.24
7	25.69	32.38	5.17	5.46
8	23.49	38.89	6.81	5.38
9	11.66	16.74	2.87	2.84
10	34.20	44.93	3.40	3.24
11	26.45	19.57	3.48	3.42
12	15.79	30.34	3.05	4.48
13	13.57	29.16	2.73	2.35
14	35.33	39.73	5.09	8.08
15	16.79	63.24	3.47	7.88
16	35.32	54.22	6.45	6.23
17	15.01	25.86	3.81	3.94
18	13.89	19.69	3.09	3.41
19	45.41	40.15	5.22	5.20
20	23.11	34.03	3.47	5.55

21	61.17	28.52	3.04	4.32
22	46.37	48.97	5.72	5.23
23	31.75	32.47	5.36	5.50
24	29.09	33.23	5.23	5.34
25	12.49	32.15	3.52	4.14
26	12.88	24.14	5.17	4.95
27	71.29	26.56	5.15	5.73
28	18.62	52.06	4.14	4.16
29	60.77	40.55	5.69	6.83
30	32.57	67.67	6.39	6.55
31	26.30	37.22	6.43	6.68
32	22.65	31.18	7.22	7.10
33	38.17	35.94	4.01	3.72
34	51.61	24.22	5.53	5.71
35	26.11	30.68	2.64	4.21
36	18.40	48.22	3.95	3.96
37	30.02	58.40	7.09	7.02
38	38.06	41.55	5.90	6.49
39	21.77	40.74	5.57	5.77
40	18.48	26.50	4.28	4.81

Appendix Table 5: Approximate entropy results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	1.335	1.199	1.824	1.768
2	1.490	1.219	1.846	1.790
3	1.528	1.276	1.729	1.685
4	1.143	0.999	1.778	1.630
5	1.251	0.838	1.418	1.289
6	1.564	1.346	1.852	1.830
7	1.261	0.896	1.646	1.336
8	1.469	1.108	1.759	1.659
9	1.230	1.272	1.739	1.624
10	1.330	1.159	1.652	1.704
11	1.324	1.196	1.793	1.762
12	1.393	1.033	1.610	1.654
13	1.426	1.126	1.564	1.479
14	1.285	1.058	1.697	1.639

15	1.376	1.090	1.670	1.622
16	1.264	0.965	1.675	1.524
17	1.266	1.146	1.838	1.741
18	1.374	0.978	1.709	1.672
19	1.521	1.190	1.741	1.677
20	1.535	1.478	1.834	1.821
21	1.180	0.968	1.548	1.635
22	1.305	0.948	1.607	1.601
23	1.188	1.157	1.826	1.764
24	1.193	0.949	1.371	1.331
25	1.392	1.009	1.778	1.770
26	1.360	1.141	1.830	1.788
27	1.510	1.228	1.827	1.843
28	1.453	1.370	1.838	1.857
29	1.106	1.072	1.678	1.681
30	1.205	0.863	1.480	1.446
31	0.933	0.916	1.849	1.886
32	1.405	1.142	1.791	1.790
33	1.266	1.036	1.728	1.599
34	1.384	1.145	1.809	1.809
35	1.290	1.159	1.875	1.852
36	1.132	1.131	1.627	1.556
37	1.306	1.158	1.836	1.826
38	1.275	1.238	1.569	1.545
39	1.281	0.984	1.433	1.490
40	1.308	0.996	1.706	1.730

Appendix Table 6: Approximate entropy results for persons with MS.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	1.354	1.154	1.821	1.647
2	1.192	0.948	1.419	1.345
3	1.233	0.912	1.890	1.832
4	1.666	1.305	1.779	1.731
5	1.397	1.176	1.745	1.774
6	1.615	1.193	1.791	1.681
7	1.148	1.079	1.700	1.572
8	1.269	1.194	1.834	1.855

9	1.420	1.225	1.787	1.778
10	0.829	0.707	1.783	1.861
11	1.323	1.248	1.726	1.725
12	1.376	1.071	1.870	1.888
13	1.537	1.253	1.629	1.826
14	1.038	1.040	1.700	1.543
15	1.510	1.375	1.867	1.751
16	1.298	1.069	1.775	1.657
17	1.472	1.287	1.821	1.755
18	1.454	1.098	1.739	1.687
19	1.130	1.090	1.776	1.763
20	1.158	1.049	1.755	1.688
21	1.173	1.314	1.867	1.817
22	1.547	1.248	1.835	1.868
23	1.114	0.906	1.748	1.642
24	1.250	1.148	1.700	1.670
25	1.343	1.151	1.783	1.756
26	1.374	1.257	1.772	1.846
27	0.904	1.049	1.625	1.642
28	1.370	1.049	1.755	1.793
29	1.266	1.348	1.659	1.635
30	1.225	0.944	1.680	1.660
31	1.296	1.098	1.774	1.702
32	1.332	1.103	1.656	1.642
33	1.029	1.075	1.766	1.717
34	0.963	1.064	1.741	1.782
35	1.505	1.201	1.893	1.844
36	1.350	1.104	1.752	1.718
37	1.483	1.165	1.692	1.731
38	0.880	0.935	1.541	1.454
39	1.254	0.903	1.649	1.424
40	1.261	1.060	1.708	1.655

Appendix Table 7: Sample entropy results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	1.189	1.388	2.037	1.914
2	1.385	1.276	2.044	1.933

3	1.618	1.338	1.833	1.682
4	0.921	1.116	1.936	1.676
5	0.680	0.362	1.381	1.236
6	1.376	1.495	2.072	1.986
7	1.301	0.608	1.662	1.267
8	1.572	1.171	1.858	1.724
9	1.369	0.782	1.803	1.611
10	1.071	1.059	1.702	1.718
11	1.538	1.090	1.924	1.844
12	1.222	1.139	1.643	1.744
13	1.167	1.194	1.562	1.501
14	0.937	0.862	1.820	1.704
15	1.268	1.316	1.726	1.629
16	1.255	0.780	1.737	1.460
17	1.184	1.282	2.016	1.836
18	1.129	0.639	1.779	1.733
19	1.183	0.824	1.899	1.694
20	1.400	1.649	2.011	1.936
21	1.001	1.027	1.428	1.624
22	1.159	0.849	1.598	1.594
23	1.128	1.112	2.041	1.875
24	0.802	1.281	1.324	1.308
25	1.066	1.142	1.943	1.906
26	1.249	1.305	1.932	1.854
27	1.504	1.371	2.008	2.009
28	1.341	1.559	2.107	2.035
29	1.130	1.226	1.716	1.722
30	1.005	1.127	1.460	1.401
31	0.967	0.781	2.051	2.052
32	1.276	0.965	1.820	1.806
33	1.172	1.105	1.785	1.549
34	1.133	1.405	1.964	1.955
35	1.264	1.349	2.098	2.020
36	0.622	1.331	1.667	1.560
37	1.342	1.301	1.959	1.935
38	0.623	1.221	1.570	1.547
39	0.972	1.284	1.372	1.442
40	1.116	1.227	1.723	1.790

Appendix Table 8: Sample entropy results for persons with MS.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	1.079	0.867	2.018	1.675
2	1.451	1.143	1.679	1.434
3	0.666	0.654	2.088	1.986
4	1.519	0.983	1.888	1.778
5	1.210	1.239	1.842	1.894
6	1.243	1.262	2.005	1.692
7	0.742	1.243	1.782	1.617
8	0.971	1.179	1.989	2.029
9	1.349	1.182	1.913	1.901
10	0.378	0.283	2.033	2.037
11	0.986	1.019	1.855	1.880
12	1.204	0.854	2.001	2.058
13	1.517	1.440	1.773	2.012
14	0.877	1.159	1.820	1.537
15	1.374	1.255	1.938	1.786
16	1.197	1.353	1.921	1.738
17	1.618	1.463	1.997	1.819
18	1.287	1.000	1.827	1.707
19	1.255	1.292	1.911	1.875
20	0.757	0.865	1.891	1.751
21	0.752	0.774	2.043	1.998
22	1.341	1.335	2.047	2.073
23	0.870	0.456	1.850	1.663
24	1.150	1.466	1.771	1.686
25	0.940	1.087	2.018	1.904
26	0.870	1.206	1.932	2.070
27	0.892	1.299	1.604	1.634
28	1.378	1.160	1.900	1.982
29	1.489	1.540	1.726	1.687
30	1.315	1.125	1.749	1.684
31	0.910	1.154	1.928	1.803
32	1.416	0.789	1.696	1.684
33	1.153	1.030	1.944	1.778
34	1.013	0.679	1.889	1.886
35	1.634	1.343	2.110	2.038
36	0.961	1.053	1.841	1.756
37	1.206	1.425	1.825	1.848
38	0.423	1.109	1.544	1.414

39	0.799	1.161	1.679	1.328
40	1.319	0.986	1.814	1.669

Appendix Table 9: Lyapunov exponent results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	0.040	0.045	0.018	0.023
2	0.042	0.047	0.020	0.017
3	0.076	0.038	0.041	0.024
4	0.023	0.031	0.007	0.006
5	0.042	0.032	0.007	0.005
6	0.048	0.053	0.039	0.022
7	0.053	0.031	0.007	0.006
8	0.075	0.037	0.010	0.008
9	0.073	0.046	0.028	0.022
10	0.039	0.053	0.024	0.011
11	0.067	0.058	0.011	0.010
12	0.043	0.047	0.018	0.014
13	0.055	0.056	0.005	0.004
14	0.057	0.051	0.005	0.009
15	0.050	0.041	0.013	0.013
16	0.053	0.050	0.010	0.009
17	0.036	0.062	0.021	0.015
18	0.071	0.034	0.013	0.012
19	0.060	0.068	0.021	0.015
20	0.049	0.058	0.026	0.026
21	0.050	0.044	0.007	0.007
22	0.041	0.050	0.007	0.010
23	0.009	0.008	0.035	0.020
24	0.034	0.028	0.004	0.007
25	0.034	0.038	0.010	0.017
26	0.039	0.050	0.011	0.007
27	0.049	0.050	0.008	0.030
28	0.088	0.085	0.078	0.035
29	0.034	0.029	0.006	0.013
30	0.039	0.035	0.007	0.007
31	0.081	0.101	0.034	0.029
32	0.052	0.028	0.016	0.015

33	0.058	0.045	0.010	0.011
34	0.058	0.051	0.017	0.016
35	0.061	0.084	0.039	0.023
36	0.047	0.082	0.008	0.008
37	0.047	0.056	0.014	0.012
38	0.045	0.043	0.005	0.007
39	0.082	0.077	0.009	0.008
40	0.041	0.046	0.008	0.013

Appendix Table 10: Lyapunov exponent results for persons with MS.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	0.056	0.027	0.029	0.023
2	0.024	0.015	0.012	0.010
3	0.066	0.030	0.062	0.056
4	0.069	0.039	0.027	0.019
5	0.076	0.021	0.038	0.023
6	0.064	0.045	0.015	0.024
7	0.026	0.032	0.008	0.010
8	0.050	0.026	0.010	0.012
9	0.024	0.016	0.016	0.013
10	0.058	0.049	0.023	0.019
11	0.051	0.049	0.024	0.032
12	0.039	0.038	0.022	0.014
13	0.042	0.023	0.012	0.015
14	0.048	0.025	0.009	0.016
15	0.048	0.029	0.024	0.015
16	0.041	0.035	0.048	0.053
17	0.045	0.046	0.012	0.016
18	0.075	0.046	0.049	0.021
19	0.084	0.054	0.025	0.042
20	0.038	0.028	0.010	0.008
21	0.040	0.023	0.049	0.012
22	0.055	0.050	0.020	0.015
23	0.067	0.052	0.021	0.023
24	0.056	0.039	0.024	0.019
25	0.091	0.060	0.018	0.025
26	0.041	0.016	0.017	0.010

27	0.042	0.040	0.047	0.047
28	0.079	0.052	0.034	0.060
29	0.051	0.022	0.011	0.016
30	0.079	0.046	0.015	0.022
31	0.059	0.033	0.026	0.022
32	0.056	0.027	0.014	0.027
33	0.052	0.038	0.011	0.011
34	0.061	0.043	0.020	0.025
35	0.046	0.026	0.010	0.015
36	0.062	0.054	0.013	0.018
37	0.053	0.024	0.009	0.011
38	0.056	0.037	0.017	0.020
39	0.077	0.032	0.017	0.032
40	0.086	0.044	0.014	0.016

Appendix Table 11: Recurrence quantification analysis %Recurrence results for healthy control subjects.

Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	0.00216	0.00851	0.00005	0.00009
2	0.00059	0.00949	0.00001	0.00005
3	0.00016	0.00548	0.00015	0.00040
4	0.01746	0.04729	0.00017	0.00110
5	0.02495	0.94108	0.00520	0.01148
6	0.00013	0.00280	0.00001	0.00005
7	0.00570	0.18631	0.00050	0.00709
8	0.00038	0.02376	0.00018	0.00064
9	0.00495	0.01390	0.00014	0.00058
10	0.00233	0.00770	0.00034	0.00023
11	0.00249	0.00927	0.00006	0.00015
12	0.00075	0.03657	0.00067	0.00056
13	0.00076	0.01720	0.00134	0.00189
14	0.00343	0.03567	0.00023	0.00069
15	0.00132	0.01718	0.00027	0.00109
16	0.00261	0.07335	0.00064	0.00273
17	0.00274	0.00917	0.00002	0.00011
18	0.00079	0.09665	0.00027	0.00075

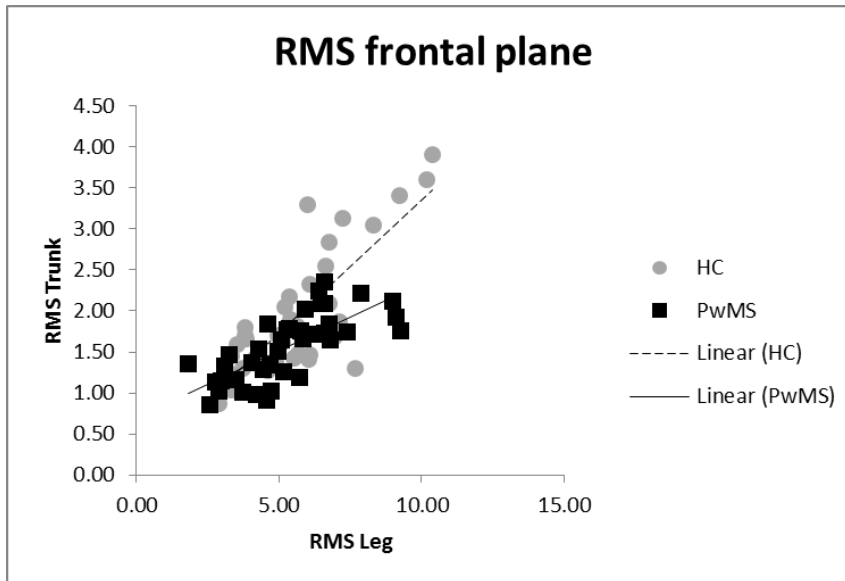
19	0.00021	0.01628	0.00018	0.00032
20	0.00016	0.00108	0.00004	0.00004
21	0.01342	0.05231	0.00305	0.00158
22	0.00186	0.06014	0.00070	0.00065
23	0.00592	0.01141	0.00002	0.00012
24	0.01199	0.04347	0.00772	0.01280
25	0.00159	0.03726	0.00009	0.00006
26	0.00278	0.01520	0.00051	0.00054
27	0.00036	0.00551	0.00002	0.00001
28	0.00053	0.00443	0.00003	0.00001
29	0.01044	0.02056	0.00050	0.00061
30	0.01153	0.09935	0.00189	0.00254
31	0.04672	0.09678	0.00001	0.00001
32	0.00074	0.01611	0.00020	0.00025
33	0.00310	0.03264	0.00019	0.00097
34	0.00171	0.01414	0.00007	0.00013
35	0.00168	0.00824	0.00001	0.00004
36	0.01800	0.01317	0.00036	0.00142
37	0.00187	0.01236	0.00005	0.00009
38	0.08338	0.01191	0.00118	0.00100
39	0.00473	0.04340	0.00287	0.00281
40	0.00252	0.04522	0.00037	0.00025

Appendix Table 12: Recurrence quantification analysis %Recurrence results for persons with MS.

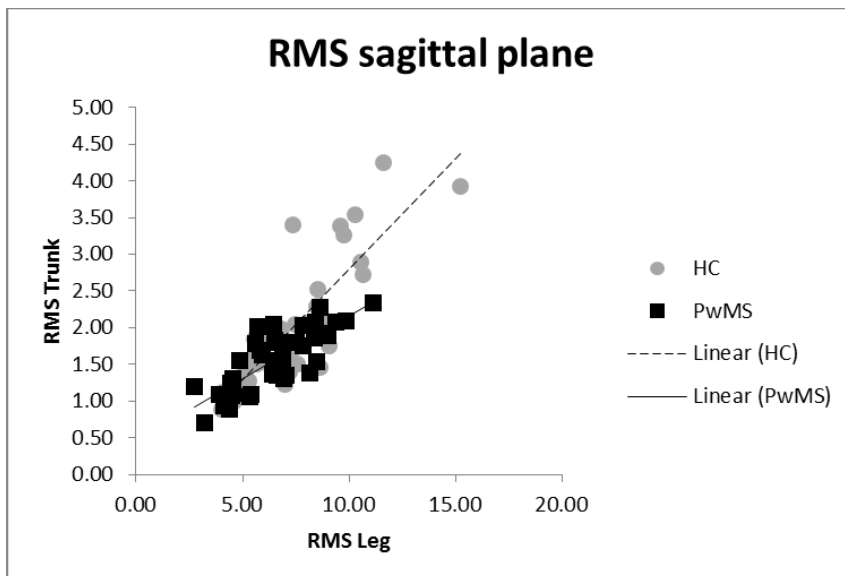
Subject #	Foot		Trunk	
	Frontal	Sagittal	Frontal	Sagittal
1	0.01013	0.00821	0.00053	0.00192
2	0.00708	0.03368	0.00897	0.00480
3	0.00224	0.00702	0.00019	0.00007
4	0.01272	0.01261	0.00134	0.00049
5	0.07741	0.03466	0.00029	0.00015
6	0.00389	0.00818	0.00723	0.00088
7	0.93990	0.07160	0.01713	0.00439
8	0.04885	0.08223	0.00802	0.00625
9	0.00974	0.01477	0.00359	0.00110
10	0.00040	0.00107	0.00088	0.00033

11	0.00450	0.00461	0.00105	0.00023
12	0.00180	0.00840	0.00173	0.00052
13	0.08463	0.02106	0.00743	0.00281
14	0.02219	0.00752	0.00087	0.00017
15	0.00285	0.00396	0.00053	0.00015
16	1.65921	2.30698	0.00142	0.00005
17	0.01241	0.00454	0.00262	0.00047
18	0.00382	0.01089	0.00056	0.00007
19	0.00081	0.00328	0.00608	0.00008
20	0.05764	0.01883	0.00739	0.00246
21	0.02696	0.00842	0.00682	0.00304
22	0.01338	0.02086	0.00232	0.00142
23	0.00243	0.00301	0.00079	0.00055
24	0.00316	0.01142	0.00131	0.00066
25	0.02091	0.01762	0.00193	0.00053
26	0.11473	0.03100	0.00512	0.00074
27	0.06619	0.00889	0.00060	0.00008
28	0.00214	0.00428	0.00077	0.00007
29	0.03058	0.14759	0.00231	0.00106
30	0.02119	0.01375	0.00505	0.00108
31	0.01245	0.00703	0.00081	0.00043
32	0.02600	0.00437	0.00095	0.00022
33	0.17754	0.02529	0.01580	0.00179
34	0.00527	0.02092	0.00168	0.00018
35	0.01375	0.00194	0.01247	0.00364
36	0.01276	0.04479	0.00517	0.00120
37	0.01597	0.01090	0.00196	0.00087
38	0.00661	0.01642	0.01069	0.00195
39	0.04814	0.01099	0.00180	0.00043
40	0.08034	0.02262	0.00193	0.00036

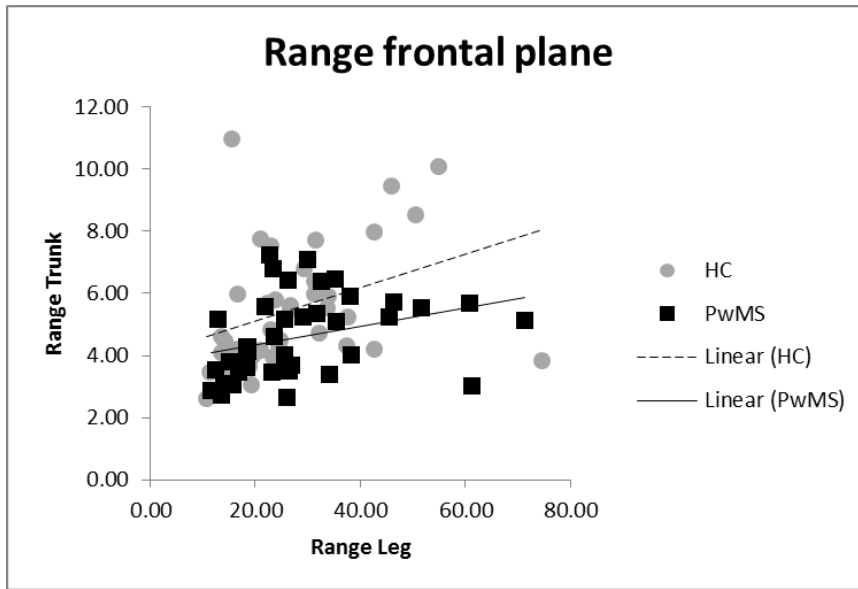
Correlation scatter plots



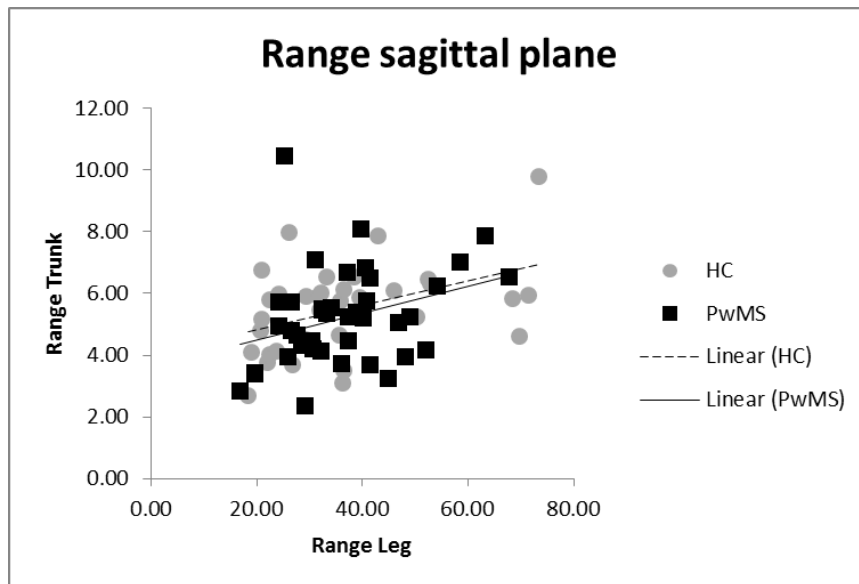
Appendix Figure 1: Relationship for RMS of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.565^*$; PwMS $r = 0.732^*$; * significance < 0.05 .



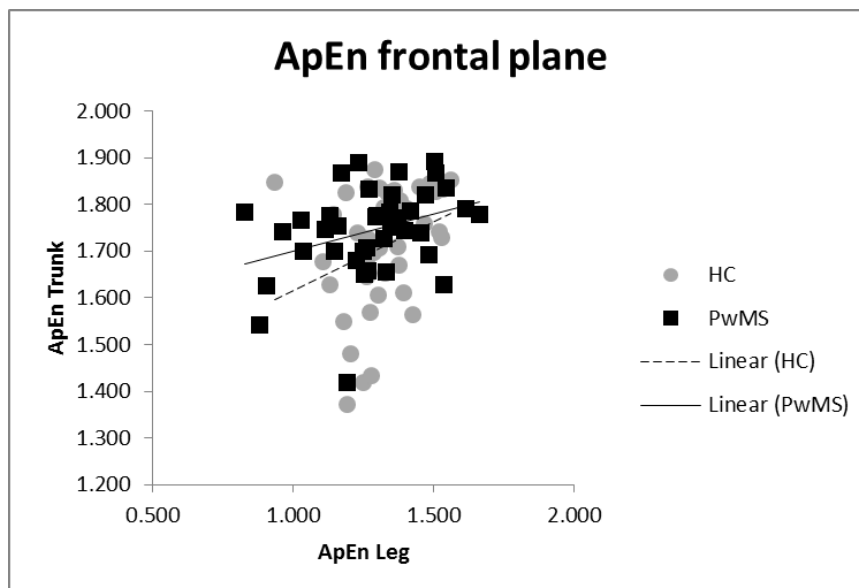
Appendix Figure 2: Relationship for RMS of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.810^*$; PwMS $r = 0.791$; * significance < 0.05 .



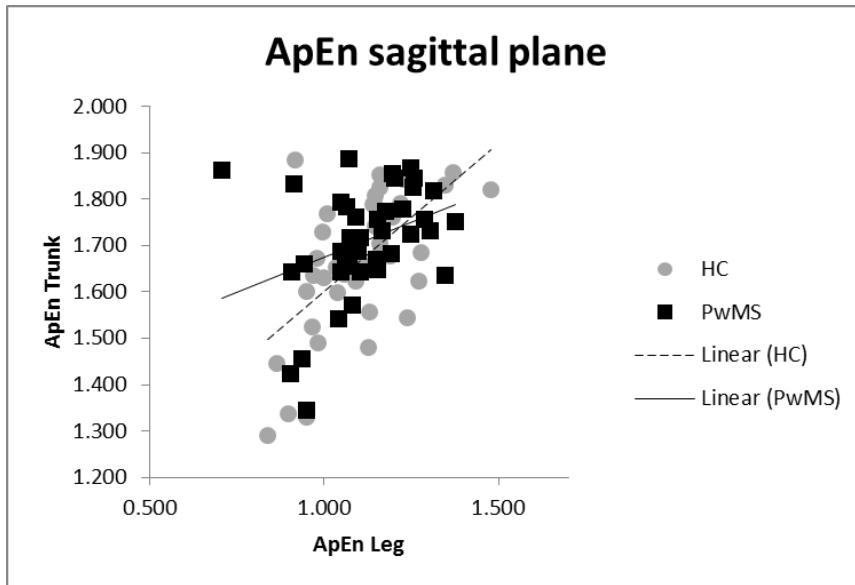
Appendix Figure 3: Relationship for range of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.711^*$; PwMS $r = 0.485^*$; * significance < 0.05 .



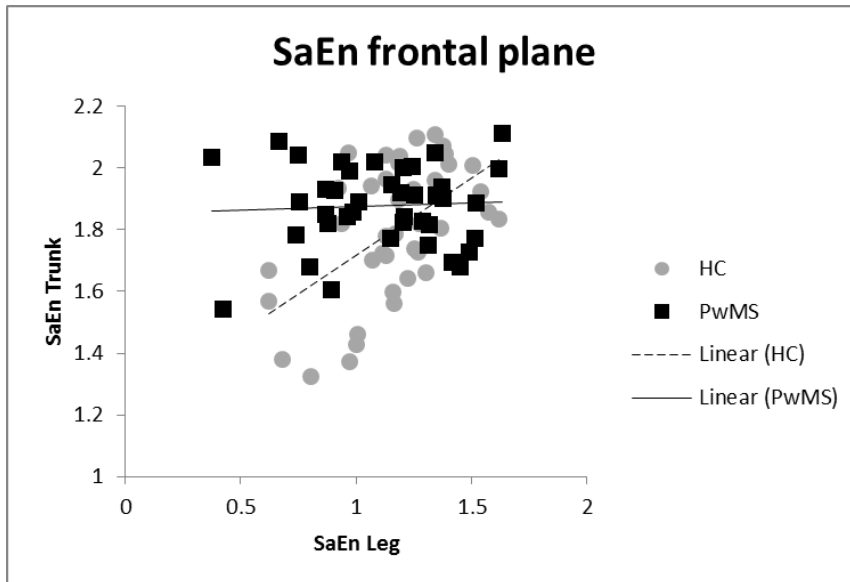
Appendix Figure 4: Relationship for range of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.274$; PwMS $r = 0.372^*$; * significance < 0.05 .



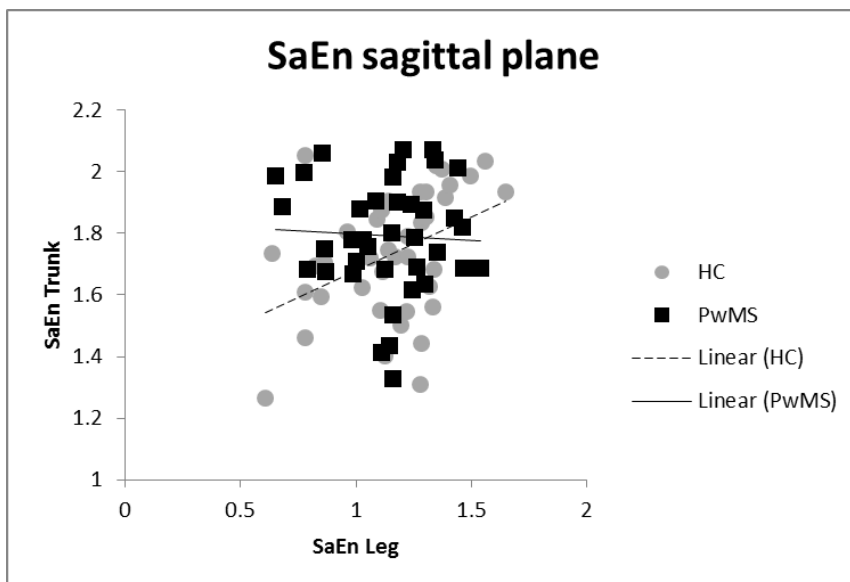
Appendix Figure 5: Relationship for ApEn of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.430^*$; PwMS $r = 0.252$; * significance < 0.05 .



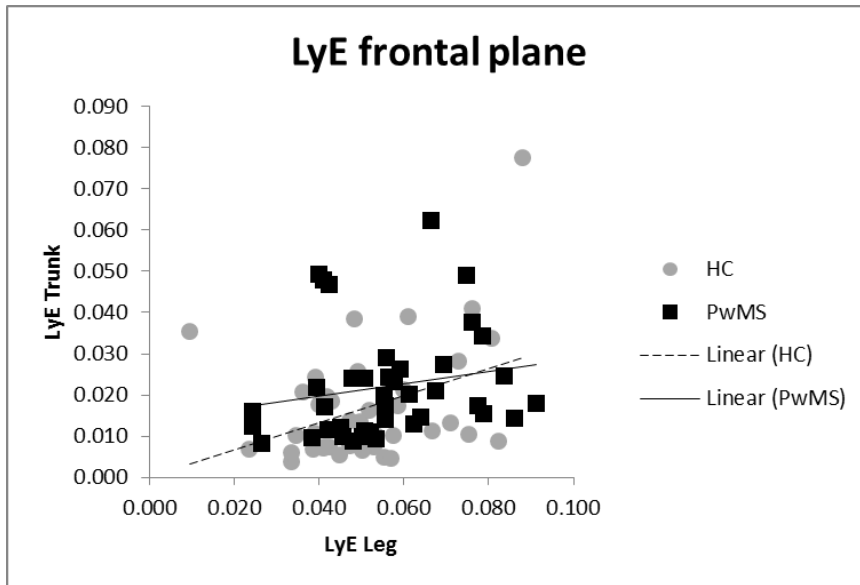
Appendix Figure 6: Relationship for ApEn of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.550^*$; PwMS $r = 0.397^*$; * significance < 0.05 .



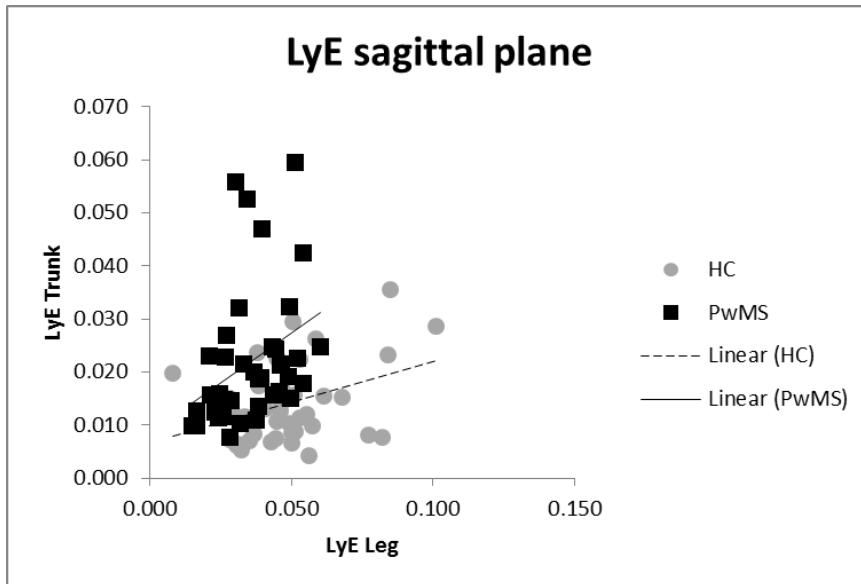
Appendix Figure 7: Relationship for SaEn of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.541^*$; PwMS $r = 0.054$; * significance < 0.05 .



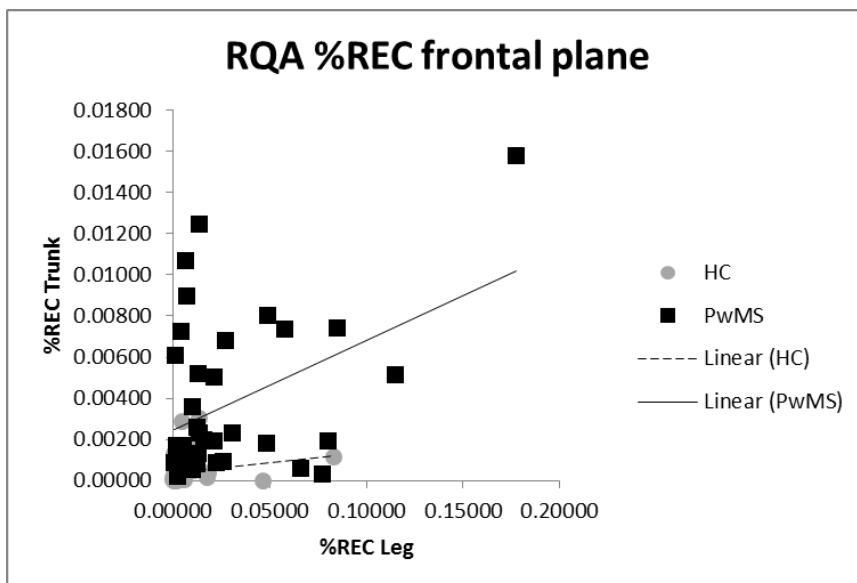
Appendix Figure 8: Relationship for SaEn of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.510^*$; PwMS $r = -0.098$; * significance < 0.05 .



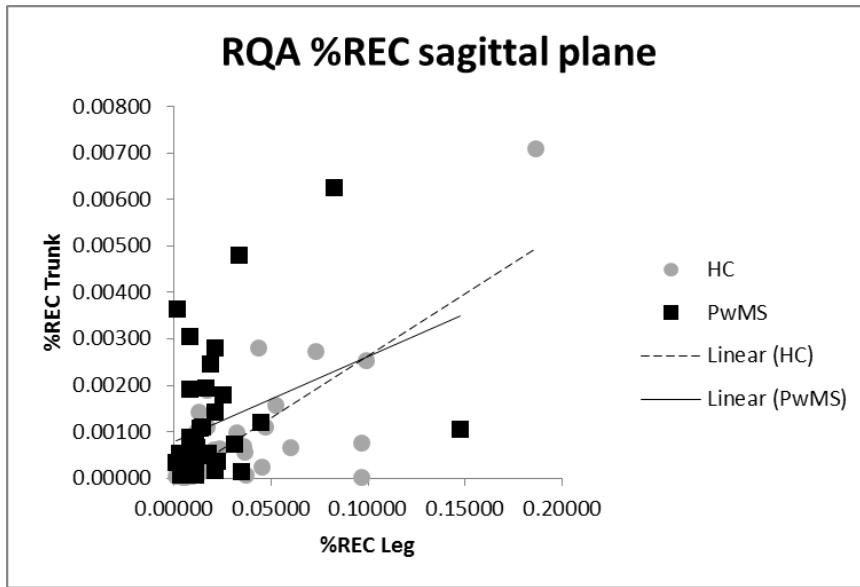
Appendix Figure 9: Relationship for LyE of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.334^*$; PwMS $r = 0.396^*$; * significance < 0.05 .



Appendix Figure 10: Relationship for LyE of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.259$; PwMS $r = 0.458^*$; * significance < 0.05 .



Appendix Figure 11: Relationship for %REC of accelerations at the foot and at the trunk in the frontal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.294$; PwMS $r = 0.284$.



Appendix Figure 12: Relationship for %REC of accelerations at the foot and at the trunk in the sagittal plane for healthy controls (gray circles, dotted line) and persons with MS (black squares, solid line). HC $r = 0.544^*$; PwMS $r = 0.310$; * significance < 0.05 .

Algorithms used for analyses

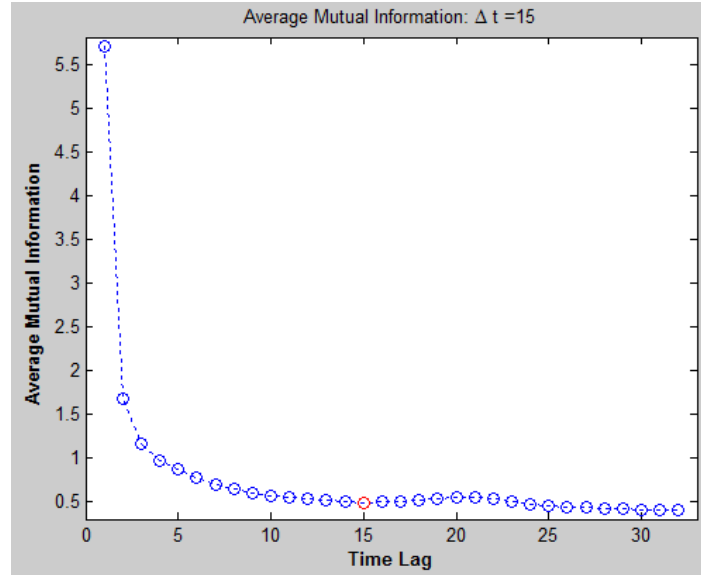
Algorithms for average mutual information (AMI) and false nearest neighbors (FNN) were developed by members of the University of Nebraska Omaha Center for Research in Human Movement Variability.

Average Mutual Information

The time lag was found by using the first minimum found by the average mutual information (AMI) algorithm. The principle behind finding the appropriate time lag is that a data point should have new information compared to the previous data point, but the points should not be so far separated from each other that they are completely independent of each other. The AMI algorithm is based around Eq. (4), where k is a variable time lag from 0 to 100, $P(x_t)$ is the probability of observing point x_t , $P(x_{t+k})$ is the probability of observing point x_{t+k} , and $P(x_t, x_{t+k})$ is the probability of observing point x_t and x_{t+k} .

$$I(k) = \sum_{t=1}^n P(x_t, x_{t+k}) \log_2 \frac{P(x_t, x_{t+k})}{P(x_t)P(x_{t+k})} \quad \text{Appendix Eq. (1)}$$

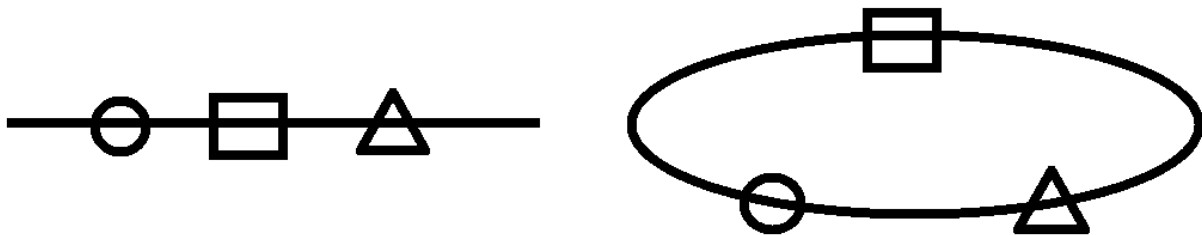
The algorithm iterates through k and plots the results as shown in Figure 4, and the time lag is selected by identifying the first minimum average mutual information in the plot.



Appendix Figure 13: *Depicted here is an example plot of average mutual information as a function of time lag. For this time series, the appropriate time lag is found to be 15.*

False Nearest Neighbors

The embedding dimension was found using the false nearest neighbors (FNN) approach. FNN are defined as sets of points that appear very close at dimension $n=k$, but not $n=k+1$ [81], a simple representation of this can be seen in Figure 5.



Appendix Figure 14: *An illustration of the concept of false nearest neighbors. In 2-dimensional space (left), it appears the square is the nearest neighbor to the circle. However, in 3-dimensional space, it is apparent that the triangle is in fact the nearest neighbor to the circle.*

The FNN algorithm takes two sequential points in dimension d and calculates the distance between a vector and its nearest neighbor in the d dimensional space (Eq. 9). The algorithm then moves up to one higher dimensional space $d+1$ and calculates the distance between the same two vectors again (Eq. 10).

$$\|V(t) - V^{NN}(t)\| \quad \text{Appendix Eq. (2)}$$

$$\|\hat{V}(t) - \hat{V}^{NN}(t)\| \quad \text{Appendix Eq. (3)}$$

If they are true neighbors, the distances will be similar in both dimensional spaces. A ratio is taken of the differences in the distances, and if the ratio is beyond a preselected tolerance R_{tol} , the vector is a false nearest neighbor (Eq. 11).

$$\frac{\|\hat{V}(t) - \hat{V}^{NN}(t)\|^2 - \|V(t) - V^{NN}(t)\|^2}{\|V(t) - V^{NN}(t)\|} > R_{tol} \quad \text{Appendix Eq. (4)}$$

The algorithm continues to cycle through dimensions 1 through 14, recording the percentage of false nearest neighbors, and plots each result. The embedding dimension is taken as the dimension at which %FN falls to approximately zero.

Matlab code used in the current study:

Code to calculate RMS and range:

```
%Last edited: Jordan Craig 8/11/15
%Root mean square and range
%-----RMS--Range-----
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=[directory_name '\'];

files=dir([directory_name, '*dat']);

if isempty(files)
```

```

        msgbox('No raw files in this directory');
    end

    for i=1:length(files)
        filename = [];
        filename = [filename; files(i).name]
        data=load([directory_name filename]);

        RMSacc(i) = rms(data);
        rangeAcc(i) = range(data);
    end

    %save, filename
        name = char(files.name);
        label = char('Filename', 'RMS', 'Range');
        c = cellstr(label);
        R = [RMSacc', rangeAcc'];
        results = [c'; cellstr(name), num2cell(R)];

        % xlswrite('RMS_Range',results);

user = getenv('USERNAME');

cd(['C:\Users\'', user, '\Desktop'])

clc
disp('Writing results...')

xlswrite('RMS_Range',results)

close all

disp('Results written to the desktop as RMS_Range.xls')

```

Code to calculate average mutual information and false nearest neighbors:

```

%Step 2
%Sample main function to obtain time delay and embedding dimension
%Last Edited: Jordan Craig 7/2/15
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\']);
files=dir([directory_name,'*.dat']);

namer = struct2cell(files);

if isempty(files)

```



```

        msgbox('No raw files in this directory')
    end
    if isempty(files)
        msgbox('No raw files in this directory')
    end

    for i = 1:length(files)

        clearvars -except allDimTau namer i directory_name

        filename=char(namer(1,i));
        data=load([directory_name filename]);

        L=32; % window size for average mutual information
        MaxDim=14; Rtol=15; Atol=2; %parameters to obtain embedding dimension

        figure(i)
        [tau,v_AMI]=AMI(data, L); %Find the first minimum average mutual
information

        [FN,dim] = FNN(data,tau,MaxDim,Rtol,Atol); %Find embedding dimension

        %AMI_plot(tau,v_AMI,L ) %Plot average mutual information

        %FN_plot(FN,dim,MaxDim) %Plot the percentage of false nearest neighbors

        allDimTau{i,1} = filename;
        allDimTau{i,2} = tau;
        allDimTau{i,3} = dim;

    end

    user = getenv('USERNAME');
    cd(['C:\Users\'', user, '\Desktop'])
    clc
    disp('Writing results...')
    xlswrite('DimTau_Results',allDimTau)
    %close all
    disp('Results written to the desktop as DimTau_Results.xls')

function [tau,v_AMI]=AMI(data, L)

%L = 32; %maximal lag -- arbitrarily selected, must be much smaller than
length(data)

N=length(data);
bins=128; %number of bins used for histogram calculation

epsilon = eps; %or use epsilon = 1e-10;

data = data - min(data); % making all the data points positive

```

```

data = 1+ floor(data/(max(data)/(bins-epsilon))); %scaling the data
v=zeros(L,1); %create a zero vector
overlap=N+1-L;
increment= 1/overlap;
one = ones(overlap,1); %create a column vector with all elements being one

% MUTUAL INFORMATION
% I (time_lag) = sum [ p(x(t), x(t + time_lag))*log[(p(x(t),p(x +
time_lag))/p(x(t))*p(x(t+time_lag)))]

%find probability p(x(t))= pA
pA = sparse (data(1:overlap),one,increment);
%e.g. when overlap = N+1-L = 6001+1-32= 5970, max(data(1:overlap))=129,
%creating a histogram with (129-1) bins
% sum(pA)= 1 --> 100 % in total

for lag = 0: L -1
    %find probability p(x(t+time_lag))=pB, sum(pB)=1
    pB = sparse(one, data(1+lag:overlap+lag), increment);
    %find joint probability p(A,B)=p(x(t),x(t+time_lag))
    pAB = sparse(data(1:overlap),data(1+lag:overlap+lag),increment);
    [A, B, AB]=find(pAB);
    v(lag+1)=sum(AB.*log2(AB./(pA(A).*pB(B)'))); %Average Mutual Information
end

v_AMI=v;
%Take time_lag when 1st min(I(time_lag))occurs for values of time_lag near
%this minimum, the coordinate system produced by time delay vector is
%essentially as good as that of the time_lag which is the actual 1st
min(I(time_lag))
for i = 1: length(v)-1
    if (find((v(i)<v(i+1))&&(v(i)<v(i-1)))) == 1
        x(i)=i;
    end
end
end

A = sparse(x);
A= find(A);
tau = A(1); % tau = 1st min(I(time_lag))

function [FN,dim] = FNN(data,tau,MaxDim, Rtol,Atol )

% Determine the embedding dimension for a time series using the false
% nearest neighbors
% References: "Determining embedding dimension for phase-space
reconstruction using
% a geometrical construction", M. B. Kennel, R. Brown, and H.D.I. Abarbanel,
% Physical Review A, Vol 45, No 6, 15 March 1992, pp 3403-3411.
% Inputs:
% data: a time series
% tau: time delay
% MaxDim: maximum embedding dimension
% Rtol: threshold for the first criterion

```

```

% Atol:      threshold for teh second criterion
% PerFFNs:   Threshold for percentage false nearest neighbors

n=length(data)-tau*MaxDim; % # of data points to be used
RA=std(data); %the nominal "radius" of the attractor

data=data';
z = data(1:n);
y = [];
FN = [];

global yq m_search L_done pqd pqr pqz b_upper b_lower sort_list node_list

m_search = 2; % just search for the nearest point; the closest will be yq
% itself and the next its neighbor

indx=[1:n];

for dim = 1:MaxDim
    y = [y; z];
    z = data(1+tau*dim:n+tau*dim);
    L = zeros(1,n);
    %fprintf('Partitioning data for dim = %d\n',dim)
    kd_part(y, z, 512); % put the data into 512-point bins <-- this needs
optimization
    %fprintf('Checking for false nearest neighbors\n')

    for i = 1:length(indx)
        yq = y(:,indx(i)); % set up the next point to check
        % set up the bounds, which start at +/- infinity
        b_upper = Inf*ones(size(yq));
        b_lower = -b_upper;
        % and set up storage for the results
        pqd = Inf*ones(1,m_search);
        pqr = [];
        pqz = [];
        L_done = 0;
        kdsearch(1); % start searching at the root (node 1)
        distance = pqz(1) - pqz(2);
        if abs(distance) > pqd(2)*Rtol
            L(i) = 1;
        end
        if sqrt(pqd(2)^2+distance^2)/RA > Atol
            L(i) = 1;
        end
    end
    FN = [FN sum(L)/n];
end

dE=FN(:,1:length(FN))';
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
for i = 2:13
    if (dE(i)==0) || ((dE(i-1)>dE(i)&&(dE(i)< dE(i+1))))
        dim(i)= i;
    end
end

```

```

        i=i+1;
    else
        i=i+1;
    end
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
dim=[];
for i = 1: 13
    %if dE(i)-dE(i+1)<=0
    if dE(i)-dE(i+1)<=0.001
        dim(i) = i;
    end
end
end
A=sparse(dim);
A=find(A);
dim=A(1);

```

Code to calculate approximate entropy:

```

%Testing null hypothesis for ApEn (Rank Test)
clear all
clc

TestType=19; % 19 for one-sided test, 39 for two-sided test at 95% confidence
level

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\\']);

files=dir([directory_name,'*dat']);

if isempty(files)
    msgbox('No raw files in this directory');
end

for i=1:length(files)
    filename = [];
    filename = [filename; files(i).name]
    data=load([directory_name filename]);

    %ApEn for original time series
    ApEn (i)= apentropy(data);
    counterA1 = 0;
    counterA0 = 0;
    %Generate 19 surrogates from the original
    APEN_A1=[]; APEN_A0=[];
    for j=1:TestType
        %Generate surrogate by Algorithm 1
        A1=theilerA1(data);
        ApEn_A1=apentropy(A1);
        APEN_A1=[APEN_A1;ApEn_A1];
    end
end

```

```

%Generate surrogate by Algorithm 0
A0=randn(size(data));
[A0,k]=sort(A0);
A0=data(k);
ApEn_A0=apentropy(A0);
APEN_A0=[APEN_A0;ApEn_A0];

%determine position of original data among the surrogates
if ApEn(i) >= ApEn_A1
    counterA1 = counterA1 +1;
end

if ApEn(i) >=ApEn_A0
    counterA0 = counterA0 +1;
end

%counter gives 5/19 (for example), but the actual position is
%6 of 20, so we will add 1 to counter and divide by 20, then
%subtract that from 1 to get the success rate.
SuccessA1(i) = 1 - ((counterA1+1)/20);
SuccessA0(i) = 1 - ((counterA0+1)/20);

%call the ApEn random surrogate function
%need to make modifications to the program to integrate with the main code
%Arand = RandApEn(data); will add later
end

%test surrogate
testA0=[ApEn(i); APEN_A0];
[permuteA0, i_permuteA0]=sort(testA0);

testA1=[ApEn(i); APEN_A1];
[permuteA1, i_permuteA1]=sort(testA1);
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% RANK TEST
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
subplot(2,1,1)
plot(permuteA0,'o')
hold on
plot(find(i_permuteA0==1),ApEn,'ro')
xlabel('Algorithm 0')
title('Rank test')
subplot(2,1,2)
plot(permuteA1,'o')
hold on
plot(find(i_permuteA1==1),ApEn,'ro')
xlabel('Algorithm 1')
title('Red circle is the ApEn of the original time series')
hold off
pause(5)
close
disp('%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%RANK
TEST%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%')
disp('Null(Algorithm 0): The data in test are i.i.d. noise')
disp('Result: ')

```

```

if find(i_permuteA0==1)~=1
    disp('ApEn value for the original time series falls in the distribution
of ApEn values of its surrogates..')
    disp('Null is not rejected (See Figure top).')
else
    disp('ApEn value for the original time series does not fall in the
distribution of ApEn values of its surrogates')
    disp('Null is rejected (See Figure top).')
end
disp('    ')

disp('Null(Algorithm 1): The data in test are produced from a linear
stochastic process.')
disp('Result:')
if find(i_permuteA1==1)~=1
    disp('Algorithm 1: ApEn value for the original time series falls in the
distribution of ApEn values of its surrogates.')
    disp('Null is not rejected (See Figure bottom).')
else
    disp('ApEn value for the original time series does not in the
distribution of ApEn values of its surrogates.')
    disp('Null is rejected (See Figure bottom).')
end
disp('%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%')
disp('%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%')

testA0
disp('Algorithm 0: The first value of testA0 is the ApEn value for the
original, and the rest are the values for its surrogates.')
disp('    ')

testA1
disp('Algorithm 1: The first value of testA1 is the ApEn value for the
original, and the rest are the values for its surrogates.')

end

%save filename, ApEn of original data, Success rate A0, A1
name = char(files.name);
label = char('Filename', 'ApEn', 'SuccessA0', 'SuccessA1');
c = cellstr(label);
R = [ApEn', SuccessA0', SuccessA1'];
results = [c'; cellstr(name), num2cell(R)];

    xlswrite('Approximate Entropy',results);

function output = apentropy(data)

% if you need to change any parameters that needs to happen in here
% these parameters are below. You can see r, m, and lag
% last modified by Jordan Craig 2/13/15

```

```

edim = 2;
lag = 6;
edata = lagembed(data,edim,lag);
[pre,post] = getimage(edata,lag);

```

```

r = .2*std(data);

```

```

output = apen(pre,post,r);

```

```

function [data2, images] = getimage(data, pred)
% [data2, images] = GETIMAGE(data,pred) finds the scalar images of
% the points in a time series <pred> time sets in the future
% data --- matrix of embedded data (from lagembed)
% pred --- look ahead time, default value 1
% Returns
% data2 --- a new embedded data matrix appropriately trimmed
% images --- the images (at time <pred>) of the points in data2
% This is a convenience program to trim an embedding appropriately.
% Copyright (c) 1996 by D. Kaplan, All Rights Reserved

```

```

if nargin < 2
    pred = 1;
end

```

```

images = data((1+pred):length(data),1);
data2 = data(1:(length(data)-pred),:);

```

```

function y = lagEmbed(x,M,lag)
% lagEmbed(x,dim,lag) constructs an embedding of a time series on a vector
% lagEmbed(x,dim) makes an m-dimensional embedding with lag 1
% lagEmbed(x,dim,lag) uses the specified lag
% Copyright (c) 1996 by D. Kaplan, All Rights Reserved

```

```

if nargin < 4

```

```

    advance=0;

```

```

end

```

```

if nargin < 3

```

```

    lag = 1;

```

```

end

```

```

%convert x to a column

```

```

[xr,xc] = size(x);

```

```

if xr == 1

```

```

    x = x';

```

```

end

```

```

lx = length(x);

newsize = lx - lag*(M-1);
y = zeros(newsize,M);
i=1;

for j = 0:-lag:lag*(-(M-1))

    first=1+lag*(M-1)+j;

    last=first+newsize-1;

    if last > lx

        last = lx;

    end

    y(:,i) = x(first:last, 1);

    i = i+1;

end

```

```

function xx=TheilerA1(s)

```

```

%plot(s)
%print -dbmp -f1 -r100 initial

N=length(s);
im=sqrt(-1);
twopi=2*pi;
half=fix((N+1.1)/2);
%Sort the original series.
%Randomize phases of the series s.
z=fft(s);
for i=2:half;
    r=rand*twopi;
    z(i)=z(i)*(cos(r)+im*sin(r));
end
for i=2:half
    z(N+2-i)=conj(z(i));
end
zz=ifft(z);
xx=real(zz);

```



```

function entropy = apen(pre, post, r)
% computer approximate entropy a la Steve Pincus

[N,p] = size(pre);

% how many pairs of points are closer than r in the pre space
phiM = 0;
% how many are closer in the post values
phiMplus1 = 0;

% will be used in distance calculation
foo = zeros(N,p);

% Loop over all the points
for k=1:N
    % fill in matrix foo to contain many replications of the point in question
    for j=1:p
        foo(:,j) = pre(k,j);
    end

    % calculate the distance
    goo = (abs( foo - pre ) <= r );

    % which ones of them are closer than r using the max norm
    if p == 1
        closerpre = goo;
    else
        closerpre = all(goo');
    end

    precount = sum(closerpre);
    phiM = phiM + log(precount);

    % of the ones that were closer in the pre space, how many are closer
    % in post also
    inds = find(closerpre);

    postcount = sum( abs( post(closerpre) - post(k) ) < r );
    phiMplus1 = phiMplus1 + log(postcount);
end

entropy = (phiM - phiMplus1)/N;

```

Matlab code for sample entropy:

```

%Last edited: Jordan Craig 8/11/15
%Entropy Step 3
%-----Sample Entropy-----
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\\']);

files=dir([directory_name,'*dat']);

if isempty(files)
    msgbox('No raw files in this directory');
end

[tauVal, tauName] = xlsread([directory_name,'DimTau_Results.xls']);

% Entropy inputs (m = vector length; R = tolerance --> R*StD(data))
m = 3;
R = 0.2;

for i=1:length(files)
    filename = [];
    filename = [filename; files(i).name]
    data=load([directory_name filename]);
    varTau = tauVal(i);
    tauUsed(i) = varTau;

%Sample for original time series
SE(i) = SampEntHPL(data, m, R, varTau);

end

%save filename, SaEn of original data, Success rate A0, A1
    name = char(files.name);
    label = char('Filename', 'sEnt', 'Tau Used', 'RMS');
    c = cellstr(label);
    R = [SE', tauUsed'];
    results = [c'; cellstr(name), num2cell(R)];

    % xlswrite('Sample_Entropy Entropy',results);

user = getenv('USERNAME');

cd(['C:\Users\'', user, '\Desktop'])

clc
disp('Writing results...')

xlswrite('Sample_Entropy',results)

close all

disp('Results written to the desktop as Sample_Entropy.xls')

```

```

function SE = SampEnt(data, m, R, varTau)
% Function to find Sample Entropy using the method described by Richman et
% al. 2000
% J McCamley 7/16/2015
% Edited by Jordan Craig 8/11/15

% Define R as r times the standard deviation
r = R * std(data);
u = data;
N = length(u);
tau = varTau;

%Jordan Craig Added time delay sections - fall 2015
for i = 1:N-m*tau
    for j = 1:N-m*tau
        for k = 1:m
            dij(k) = abs(u(i+((k-1)*tau))-u(j+((k-1)*tau)));
        end
        di(j) = max(dij);
    end
    d = find(di<=r); % find the vectors that are less than "r" distant from
one another
    nm = length(d)-1; % subtract the self match
    Bm(i) = nm/(N-(m*tau)-1);
end
Bmr = sum(Bm)/(N-(m*tau));

for i = 1:N-m*tau
    for j = 1:N-m*tau
        for k = 1:m+1
            dij(k) = abs(u(i+((k-1)*tau))-u(j+((k-1)*tau)));
        end
        di(j) = max(dij);
    end
    d = find(di<=r); % find the vectors that are less than "r" distant from
one another
    nm = length(d)-1; % subtract the self match
    Am(i) = nm/(N-(m*tau)-1);
end
Amr = sum(Am)/(N-(m*tau));

B = (((N-(m*tau)-1)*(N-(m*tau)))/2)*Bmr;
A = (((N-(m*tau)-1)*(N-(m*tau)))/2)*Amr;
SE = -log(A/B);
end

```

Matlab code to run Lyapunov Exponent:

```

% Code to find the Lyapunov exponent for a selected data series using the
% Wolf algorithm and input values of Tau and Embedding Dimension
% John McCamley - 7/16/2015

```

```

% For this code to run it requires the files in the folder "LyE_Wolf" to
% be in the Matlab path
% Edited by Jordan Craig - 10/14/2015
% To run batch folders with xls doc assigning tau

clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=[directory_name '\'];

files=dir([directory_name,'*dat']);

if isempty(files)
    msgbox('No raw files in this directory');
end

[tauVal, tauName] = xlsread([directory_name,'DimTau_Results.xls']);

% input embedding dimension for batch
input1 = 'Enter the embedding dimension for this data? ';
dim = input(input1);

for i=1:length(files)
    filename = [];
    filename = [filename; files(i).name]
    data=load([directory_name filename]);
    varTau = tauVal(i);
    tauUsed(i) = varTau;

%LyE
LyE(i)=Lyapunov(data,dim,varTau);

end

%save / output .xls doc
name = char(files.name);
label = char('Filename', 'LyE', 'Tau Used');
c = cellstr(label);
R = [LyE', tauUsed'];
results = [c'; cellstr(name), num2cell(R)];

user = getenv('USERNAME');

cd(['C:\Users\'', user, '\Desktop'])

clc
disp('Writing results...')

xlswrite('LyE_Wolf_Results',results)

close all

disp('Results written to the desktop as LyE_Wolf_Results.xls')

```

```

function LyE=Lyapunov(X,dim,tau)

% dim: embedding dimension
% tau: time lag
% DT: time between data samples required only for normalization of the
%      exponent
% A: relative accuracy of the data below which noise is expected to
%      dominate
% SCALMX: length scale on which the local structure of attractor is no
%      longer being probe
% n: number of sample intervals over which each pair of points is followed
%      before a new pair is chosen. If n is too large teh trajectories get
too
%      far apart and the exponential divergence of the orbit is lost.
% IND: initial points to fiducial trajectory

%change paramters here

DT=1;
A= 10^(-4);
SCALMX=(max(X)-min(X))/10;
n=3;
IND=1;

LyE=LyE_Wolf(X,dim,tau,DT,A,SCALMX,n,IND);

function [x,y] = embed(z,v,w)

% [x,y] or x= embed(z,lags) or embed(z,dim,lag)
% embed z using given lags or dim and lag
% embed(z,dim,lag) == embed(z,[0:lag:lag*(dim-1)])
% negative entries of lags are into future
%
% If return is [x,y], then x is the positive lags and y the negative lags
% Order of rows in x and y the same as sort(lags)
%
% defaults:
%   dim = 3
%   lag = 1
%   lags = [0 1 2]; or [-1 lags] when two outputs and no negative lags

% Copyright (c) 1994 by Kevin Judd.
% Please see the copyright notice included in this distribution
% for full details.
%
% NAME embed.m
%   $Id$

if nargin==3
    v= 0:w:w*(v-1);
end;

```

```

if nargin==1
    v= [0 1 2];
end
if nargin==2 & min(v)>=0
    v= [-1 v];
end
lags= sort(v);

dim = length(lags);

[c,n] = size(z);
if c ~= 1
    z = z';
    [c,n] = size(z);
end
if c ~= 1
    error('Embed needs a vector as first arg.');
```

end

```

if n < lags(dim)
    error('Vector is too small to be embedded with the given lags');
```

end

```

w = lags(dim) - lags(1);           % window
m = n - w;                         % Rows of x
t = (1:m) + lags(dim);            % embed times

x = zeros(dim,m);

for i=1:dim
    x(i,:) = z( t - lags(i) );
end

if nargin==2
    id= find(v<0);
    y= x(id,:);
    id= find(v>=0);
    x= x(id,:);
end;
```

function ZLAP=LyE_Wolf(X,dim,tau,DT, SCALMN, SCALMX, EVOLV,IND)

```

[r c]=size(X);
if c > r
    X=X';
end

SUM=0.0; % Sum holds running exponent estimate sans 1/time;
ITS=0; % total number of propagation steps

NPT=length(X)-dim*tau-EVOLV; %Calculate useful size of data

%Find nearest neighbor to first data point
```

```

DI=1.e38;

%Dont take point too close to fiducial point

for i=11:NPT
    %Compute separation between fiducial point and candidate
    D=0;
    for j=1:dim
        D=D+(X(IND+(j-1)*tau)-X(i+(j-1)*tau))^2;
    end
    D=sqrt(D);

    %Store the best point so far but no closer than noise scale
    if (D <= DI) && (D >= SCALMN)
        DI=D;
        IND2=i;
    end
end

while (IND < NPT)
    %get coordinates of evolved points
    PT=GetCoordinate(X,IND,IND2,EVOLV,dim,tau);
    PT1=PT(:,1)';
    PT2=PT(:,2)';
    %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
    %Plot
    %SensitiveDependenceIC(X,dim,tau,IND,IND2,EVOLV)
    %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
    %compute final separation between pair, update exponent
    DF=0;
    for j=1:dim
        DF=DF+(PT1(j)-PT2(j))^2;
    end
    DF=sqrt(DF);

    ITS=ITS+1;
    SUM=SUM+log(DF/DI)/(EVOLV*DT);

    ZLAP=SUM/ITS;

    %Look for replacement point
    %ZMULT is multiplier of SCALMX when go to longer distances
    INDOLD=IND2;
    ZMULT=1;
    ANGLMX=0.3;
    THMIN=3.14;

    %Search over all points
    [DII IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1, PT2,SCALMX, ZMULT,
SCALMN,DF,ANGLMX,INDOLD);

    IND=IND+EVOLV;
    DI=DII;
end
ZLAP;

```

```
function [DII, IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1, PT2,SCALMX,
ZMULT, SCALMN, DF,ANGLMX,INDOLD)
```

```
    THMIN=3.14;
    NPT=length(X)-dim*tau-EVOLV;
    for i=1:NPT
        III=abs(i-(IND+EVOLV));
        if (III >= 10)
            DNEW=0;
            for j=1:dim
                DNEW=DNEW+(PT1(j)-X(i+(j-1)*tau))^2;
            end
            DNEW=sqrt(DNEW);

            %look further away than noise scale, closer than ZMULT*SCALM
            if (DNEW <= ZMULT*SCALMX)&&(DNEW >= SCALMN)
                %Find angular change old to new vector
                DOT= sum((PT1'-X(i+(1:dim)-1)*tau)).*(PT1'-PT2'));
                CTH=abs(DOT/(DNEW*DF));
                if (CTH > 1.0)
                    CTH=1.0;
                end
                TH=acos(CTH);
                %Save point with smallest angular change so far
                if (TH <= THMIN)
                    THMIN=TH;
                end
                DII=DNEW;
                IND2=i;
            end
        end
    end

    if (THMIN >= ANGLMX)
        [DII, IND2]=LookLongerDistance(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN,DF, ANGLMX,INDOLD);
    end
```

```
function PT=GetCoordinate(X,IND,IND2,EVOLV,dim,tau)
```

```
    if min((length(X)>IND+EVOLV+((1:dim)-1)*tau))&&
min((length(X)>IND2+EVOLV+((1:dim)-1)*tau))
        PT1=[X(IND+EVOLV+((1:dim)-1)*tau)]';
        PT2=[X(IND2+EVOLV+((1:dim)-1)*tau)]';
        PT=[PT1' PT2'];
    else
        disp('Exceeds the length of X')
    end
```

```
function [DII, IND2]=LookLongerDistance(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN,DF, ANGLMX,INDOLD)
```



```

%Can't find a replacement -- look at longer distances
ZMULT = ZMULT+1;
if (ZMULT<5)
    [DII,IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1, PT2,SCALMX, ZMULT,
SCALMN,DF,ANGLMX,INDOLD);
    %disp('here1')
else
    % No replacement at 5*SCALE, double search angle, reset
    % distance
    ZMULT=1.0;
    ANGLMX=2*ANGLMX;
    if (ANGLMX < 3.14)
        [DII,IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1, PT2,SCALMX, ZMULT,
SCALMN,DF,ANGLMX,INDOLD);
    else
        IND2=INDOLD+EVOLV;
        DII=DF;
    end
end
end

```

Matlab code to run recurrence quantification analysis:

```

function aRQA_batch()
%
*****
*****
%   function aRQA_batch()
%
%   Performs a batch Auto Recurrence Quantification Analysis
%
%   M.J. Richardson 7/2004, updated 2009, 2015
%
%-----
-----
fprintf('Processes xRqa on txt files\n');

% Get User Input for Parameters and File Settings
dirtxt_prim = input('Enter primary .txt or .csv file pattern (wildcards, but
NO EXTENSION): ','s');
ext1 = input('Enter file extension (e.g. .txt or .csv): ','s');
norm = input('Normalize data (0=none, 1=unit interval, 2=zscore, 3=center):
');
Edim = input('Embedding dimen: ');
Tlag = input('Time lag: ');
rescale = input('Rescale option (1=mean 2=max): ');
radius = input('Radius: ');
doStatsFile = input('Output stats to file (1=yes, 0=no):' );

if isempty(strfind(dirtxt_prim, '.'))
    dirtxt_prim = strcat(dirtxt_prim,ext1);
end
dir_in_prim=dir(dirtxt_prim);
nfiles_prim = length(dir_in_prim);

if nfiles_prim==0

```

```

        fprintf('No %s files found\n',ext1);
        return
    end

    fns_prim = sortfiles(dir_in_prim);

    fprintf('\n\n%d file(s) to process... ... \n',nfiles_prim);

    for i = 1:nfiles_prim
        file_name = fns_prim(i,:);
        file_name = deblank(file_name);

        aRQA(file_name, norm, Edim, Tlag, rescale, radius, 0, doStatsFile);

    end

    fprintf('\nDone!\n');
    return;

%*****
function sorted_names = sortfiles(direc);
%function sorted_names = sortfiles(direc);
%Sort a list of file names
%M.J. Richardson 2004
ld = length(direc);
[fn{1:ld,1}] = deal(direc.name);
sorted_names = char(fn);
sorted_names = sortrows(sorted_names);
return

function aRQA(filename, norm, eDim, tLag, rescale, radius, doPlots,
doStatsFile)
%
%*****
%*****
%    function aRQA(filename, norm, eDim, tLag, rescale, radius, doPlots,
doStatsFile)
%
%    Performs auto Recurrence Quantification Analysis
%
%    Inputs:
%        filename      : data file; must be txt or csv file with no headers
%        norm          : data normalization(0=none, 1=unit interval,
2=zscore, 3=center)
%        Edim          : embedding dimension
%        Tlag           : time lag
%        rescale        : radius rescale option (1=mean distance 2=max
distance)
%        radius         : recurrence radius
%        doPlots        : 1=yes, 0=no
%        doStatsFile    : 1=yes, 0=no
%
%    Syntax Example:
%        aRQA('datafile.txt', 1, 3, 15, 1, 10, 1, 1)
%

```

```

% Output stats file column:
%     filename, eDim, tLag, rescale, radius, %REC, %DET, Maxline,
MeanLine, Entropy
%
%   BY: Bruce Kay 2003-2005 UCONN
%       Michael J. Richardson 2004-2005, updated 2009, 2015, UC
%
%   NOTE: Using sub-routines developed by Bruce Kay and Michael Richardson
%         at UCONN from 2003 to 2005.
%
%   Contact: michael.richardson@uc.edu
%-----
-----

%% Fixed Parameters: Change if needed.
tmin = 2; % remove line of identity for auto recurrence
minl = 2; % min number of points for a line; effects %DET and MeanLine

%% Check radius input
if radius >= 1
    radius = radius/100; %convert to decimal
end

%% Load data form file; should be single column file
Data_raw = load(filename);
DataX = Data_raw(:,1);

%% Normalize to common range
if (norm == 1)
    % (0 to 1)
    DataX = (DataX-min(DataX))/(max(DataX)-min(DataX));
elseif (norm == 2)
    % zscore
    DataX = zscore(DataX);
elseif (norm == 3)
    % center around the mean
    DataX = DataX-mean(DataX);
else
    % do nothing and leave data as is.
end;

%% Perform RQA stuff
ds = xRQA_dist(DataX,DataX,eDim,tLag);
[td, rs, ~, err_code] = xRQA_stats(ds.d,rescale,radius,tmin,minl);

if err_code == 0
    fprintf('%s      REC: %2.3f      DET: %3.3f      MxL: %5.2f\n',
filename, rs.perc_recur, rs.perc_determ, rs.maxl_found);
else
    fprintf('%s      REC: 0.000      DET: 0.000      MxL: 0.000\n',
filename);
end;

%% Do Plots
if doPlots == 1
    close all;
    scrsz = get(0,'ScreenSize');

```

```

figure('Position',[scrsz(3)/4 scrsz(4)/4 scrsz(3)/3 scrsz(4)/2]);
h = axes('Position', [0 0 1 1], 'Visible', 'off');

axes('Position',[.375 .35 .58 .6], 'FontSize', 8)
image(rot90(td*25)); % invert color
xlabel('X(i)', 'Interpreter', 'none', 'FontSize', 10);
ylabel('X(j)', 'Interpreter', 'none', 'FontSize', 10);
set(gca, 'XTick', [ ]);
set(gca, 'YTick', [ ]);

axes('Position',[.375 .1 .58 .15], 'FontSize', 8)
plot(1:length(DataX), DataX, 'b-');
xlim([1 length(DataX)]);

axes('Position',[.09 .35 .15 .6], 'FontSize', 8)
plot(DataX, 1:length(DataX), 'b-');
ylim([1 length(DataX)]);

set(gcf, 'CurrentAxes', h);
str(1) = ['%REC = ', sprintf('%.2f',rs.perc_recur)]];
text(.05, 0.24, str, 'FontSize', 10, 'Color', 'b');
str(1) = ['%DET = ', sprintf('%.2f',rs.perc_determ)]];
text(.05, .20, str, 'FontSize', 10, 'Color', 'b');
str(1) = ['%MAXLINE = ', sprintf('%.0f',rs.maxl_found)]];
text(.05, .16, str, 'FontSize', 10, 'Color', 'b');
str(1) = ['%MEANLINE = ', sprintf('%.0f',rs.llmnsd(1))]];
text(.05, .12, str, 'FontSize', 10, 'Color', 'b');
str(1) = ['%ENTROPY = ', sprintf('%.2f',rs.entropy(1))]];
text(.05, .08, str, 'FontSize', 10, 'Color', 'b');

end;

%% Print Output Stats
if doStatsFile > 0
    fid = fopen('RQA_Stats.csv','a');
    fprintf(fid,'%s',filename);
    fprintf(fid,'%d, %d,%d, %f, ',eDim, tLag, rescale, radius*100);
    if err_code == 0
        fprintf(fid,'%f,%f,%f,%f,%f\n',rs.perc_recur, rs.perc_determ,
rs.maxl_found, rs.llmnsd(1), rs.entropy(1));
    else
        fprintf(fid,'0.0,0.0,0.0,0.0,0.0\n');
    end
    fclose(fid);
end

%% End of Function
return;

function [ds,err_code] = xRQA_dist(a,b,dim,lag)

%*****
% FUNCTION [ds,err_code] = xRQA_dist(a,b,dim,lag);
%
% Compute distances between all points of two vectors,

```

```

% which can be embedded using time-lags. (The Webber method of PSR for
xrQA).
% For recurrence plots.
%
% Input:
%   a, b   -- data vector (1XN or NX1)
%   dim -- embedding dimension (scalar)
%   lag -- time lag in samples (scalar)
%
% Output:
%   ds -- structure containing the input parameters dim & lag
%        and the distance matrix (ds.d). (Type the structure name
%        to see the list.)
%        Send ds.d to xrqa_do to do the thresholding, etc.
%
% Note: any errors in the input arguments causes the function
% to print an error message to the screen and return dist = 0 (scalar).
%-----
-----

%% Check input arguments
% Make sure the data vectors are column and of the same length
if size(a,1) < size(a,2)
    a = a';
end

if size(1) < size(2)
    b = b';
end

if size(a,2) ~= 1
    fprintf('Input a data must be a vector, not a matrix\n');
    err_code = 1;
    ds = 0;
    return;
end

if size(b,2) ~= 1
    fprintf('Input b data must be a vector, not a matrix\n');
    err_code = 2;
    ds = 0;
    return;
end

if size(a,1) ~= size(b,1)
    fprintf('Vectors are of different length\n');
    err_code = 3;
    ds = 0;
    return
end

n = size(a,1);

if ~all(size(dim) == [1 1])
    fprintf('Please use a scalar embedding dimension\n');
    err_code = 4;
    ds = 0;

```

```

        return;
    end

    if mod(dim,1) ~= 0
        fprintf('Please use integer embedding dimension\n');
        err_code = 5;
        ds = 0;
        return;
    end

    if dim <= 0
        fprintf('Please use an embedding dimension >= 1\n');
        err_code = 6;
        ds = 0;
        return;
    end

    if ~all(size(lag) == [1 1])
        fprintf('Please use a scalar timelag\n');
        err_code = 7;
        ds = 0;
        return;
    end

    if mod(lag,1) ~= 0
        fprintf('Please use integer timelag\n');
        err_code = 8;
        ds = 0;
        return;
    end

    if lag <= 0
        fprintf('Please use a time-lag >= 1\n');
        err_code = 9;
        ds = 0;
        return;
    end

    n2 = n - lag*(dim-1);
    if n2 <= 0
        fprintf('Not enough data for these embedding parameters\n');
        err_code = 10;
        ds = 0;
        return;
    end

    err_code = 0;

    %% Initialize needed matrices
    dist = zeros(n2,n2,'single');
    v = zeros(n2,dim,'single');

    %% Calculate Distance Matrix
    if dim > 1
        % Embed if requested
        emb_a=zeros(n2,dim,'single');

```

```

emb_b=zeros(n2,dim,'single');
for k=1:dim
    emb_a(:,k) = a((1:n2)+lag*(k-1));
    emb_b(:,k) = b((1:n2)+lag*(k-1));
end

% Compute embedded case
for i = 1:n2
    for k = 1:dim
        v(:,k) = emb_a(i,k) - emb_b(:,k);
    end
    v = v.^2;
    dist(i,:) = sqrt(sum(v(:,1:dim)'));
end
else

    % Compute non-embedded case
    for i = 1:n2
        dist(i,:) = (abs(a(i) - b))';
    end

end

ds = struct('dim',dim,'lag',lag,'d',dist);

return;

function thrd = xRQA_radius(dist,rescale,rad,tmin)

%*****
%*****
% FUNCTION thrd = xRQA_radius(dist,rescale,rad,tmin);
%
% Finds all points in distance matrix less than or equal to rad
% For recurrence plots
%
% Inputs:
%   dist -- square (NXN) distance matrix, w/distances only on the upper
diagonal
%   rescale -- 1 = use mean dist to rescale, 2 = use max dist
%              anything else = don't rescale (Webber's "absolute" option)
%   region -- 1 = use entire distance matrix anything else = use "diamond"
%   rad -- distance threshold; meaning of value depends on rescale option
%   tmin -- min recurrence time: points are recurrent iff they are
%           >= tmin samples apart; this eliminates tmin-1 diagonals off the
%           main one. (Because recurrence should not be due to continuous
%           dynamics.)
%   plotopt -- 1 = do recurrence plot, otherwise don't
%
% Output
%   thrd -- thresholded distance matrix, having same dimensions as dist,
%           but with 1's where distance <= rad and 0's elsewhere, and both
%           upper and lower diagonal portions.
%           Points inside the Theiler window (set by tmin) are set to 0
(nonrecurrent).
%
% Note: any errors in the input arguments causes the function

```

```
% to print an error message and return thrd = -1 (scalar).
```

```
%-----  
-----
```

```
%% Check input arguments
```

```
s=size(dist);
```

```
if s(1) ~= s(2)
```

```
    fprintf('Distance matrix must be square\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
if s(1) == 1
```

```
    fprintf('Distance matrix has only one element!\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
s=size(rad);
```

```
if ~all(s == [1 1])
```

```
    fprintf('Please use a scalar threshold\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
if rad <= 0
```

```
    fprintf('Please use a threshold > 0\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
s=size(rescale);
```

```
if ~all(s == [1 1])
```

```
    fprintf('Please use a scalar rescale parameter\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
s=size(tmin);
```

```
if ~all(s == [1 1])
```

```
    fprintf('Please use a scalar tmin parameter\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
if mod(tmin,1) ~= 0
```

```
    fprintf('Please use integer tmin\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```

```
if tmin < 0
```

```
    fprintf('Please use a tmin >= 0\n');
```

```
    thrd = -1;
```

```
    return;
```

```
end
```



```

%% Rescale distance matrix
if rescale == 1
    mn = mean(mean(dist));
    dist = dist/mn;
elseif rescale == 2
    mx = max(max(dist));
    dist = dist/mx;
end

%% Perform thresholding
%Nonvectorized algorithm: actually faster almost all of the time for this
single-precision algorithm
ldist = length(dist);
thrd = zeros(ldist,ldist,'int8');
for i = 1:ldist
    for j = 1:ldist
        if dist(i,j) <= rad
            thrd(i,j) = 1;
        end
    end
end

%% Set distances within tmin as non-recurrent
if tmin ~= 0
    lt = length(thrd);
    for i = 0:tmin-1
        for j = 1:lt-i
            thrd(j,j+i) = 0;
            thrd(j+i,j) = 0;
        end
    end
end

return

function [ll,maxl_poss,npts,trend1,trend2] = xRQA_line(thrd,tmin)

%*****
%*****
% FUNCTION [ll,maxl_poss,npts,trend1,trend2] = xRQA_line(thrd,tmin);
%
% Single-precision version of xrqa_line1.m; works only with Matlab R14+
%
% Find all diagonal lines (parallel to the main diagonal) and their lengths
in a thresholded distance matrix.
% Do so for ENTIRE recurrence plots (compare xrqa_line2_single). Also
computes TRENDS.
%
% Input:
%   thrd -- square thresholded distance matrix having 1's and 0's at least
on the upper diagonal
%   tmin -- minimum recurrence time (retain main diagonal if == 0); sets the
Theiler window
%   plotopt -- plotting option (TREND: recurrence as function of distance
from main diagonal) (1=yes, other = no)
%

```

```

% Output:
% ll -- vector containing the lengths of all the lines found, even those
>= 1 and < minl
% max_poss -- maximum possible line length
% npts -- total number of possible points in the recurrence plot,
excluding the Theiler window
% trend1 -- Webber's Trend measure for one triangle of the threshold
matrix
% trend2 -- " for the other triangle of the threshold matrix
%
% Note: any errors in the input argument causes the function
% to print an error message and return all outputs = 0.
%-----
-----

%% Check input matrix
s=size(thrd);
if s(1) ~= s(2)
    fprintf('Thresholded distance matrix must be square\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;
    return;
end

if s(1) == 1
    fprintf('Thresholded distance matrix has only one element!\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;
    return;
end

mx = max(max(thrd));
if mx > 1
    fprintf('Please use a thresholded distance matrix\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;
    return;
end
n = s(1);

s=size(tmin);
if ~all(s == [1 1])
    fprintf('Please use a scalar tmin parameter\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;

```

```

        return;
end

if mod(tmin,1) ~= 0
    fprintf('Please use integer tmin\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;
    return;
end

if tmin < 0
    fprintf('Please use a tmin >= 0\n');
    ll = 0;
    trend1 = 0;
    trend2 = 0;
    maxl_poss = 0;
    npts = 0;
    return;
end

% Compute; very slow if lots of long lines, but at least it works correctly
% The following "brute force" method seems inefficient, but it's the fastest
thing I've tried.
% See count_lines.m & xrqa_lines1_single_b.m for another algorithm.

possuml1 = ceil((n^2)/2); nlines = 0;
recur = zeros(2*n-1,2,'single');
%recur = zeros(2*n-1,2);

ll = zeros(possuml1,1,'int16'); %line lengths found; this seems to be a
reasonable guess as to the max possible # of found lines,
%but we may need to change this.
nlines = 0;
for i = 1:2*n-1 %Does all diagonals, for cross-recurrence case
    d = diag(thrd,i-n);
    ld = length(d);
    recur(i,1) = ld;
    recur(i,2) = 0; %Total recurrence along ith diagonal

    j = 1;
    while j <= ld

        if d(j) == 1
            nlines = nlines + 1;
            ll(nlines) = 1;
            recur(i,2) = recur(i,2)+1;

            k=j+1;
            while k <= ld

                if d(k) == 1
                    ll(nlines) = ll(nlines) + 1;
                    recur(i,2) = recur(i,2)+1;
                    k = k + 1;
                end
            end
        end
        j = j + 1;
    end
end

```

```

                else
                    break
                end

            end
            j=k+1;

        else
            j=j+1;
        end
    end
end

% Shrink ll to actual # of lines found
if nlines > possnumll
    fprintf('***Please increase possnumll in xrqa_line1.m!***\n');
    fprintf('Initialized line length vector size exceeded, performance
greatly reduced!\n');
end

ll = ll(1:nlines);

% Compute trend
% Acc. to Weber, = slope of line-of-best fit through percentrecurrence
% as a function of displacement from main diagonal, excluding the last
% ten percent of the range, in units of percent recurrence (locally
% measured) per 1000 points ("points"=distance from main diagonal).
% Do it for the upper & lower diagonal matrices and average

mid = find(recur(:,1) == max(recur(:,1)));

recur(:,2) = recur(:,2)./recur(:,1);

% lower:
first = tmin;
last = n-1;
indx = (first:last)';

p = polyfit(indx,100*recur(mid-tmin:-1:1,2),1);
trend1 = 1000*p(1);
% upper:
first = mid+tmin;
last = 2*n-1;

p = polyfit(indx,100*recur(first:last,2),1);
trend2 = 1000*p(1);

lmd = length(thrd);
maxl_poss = lmd - tmin;
if tmin == 0
    npts = lmd^2;
else %Total number of points in the recurrence plot, excluding the diagonals
taken up by tmin
    npts = lmd^2 - lmd - 2*lmd*(tmin-1) + tmin*(tmin-1);
end

return

```

```

function [linehist,linestats] = xRQA_histlines(llengths, minl)

%*****
%*****
% FUNCTION [linehist,linestats] = xRQA_histlines(llengths, minl);
%
% Inputs:
%   llengths -- vector of line lengths
%   minl -- minimum line length to consider
%   plotopt -- 1 = do plots of line length histogram
%               subplot 1: linear scaling on both axes
%               subplot 2: log scaling on both axes
%
% Output:
%   linehist -- NX2 matrix for doing histogram of line lengths a la Webber
%               (N=# of distinct line lengths found)
%               column 1 = line length
%               column 2 = frequency
%               Contains only the line lengths >= minl
%   linestats -- mean, SD, and N of line lengths >= minl
%
% Note: any errors in the input arguments causes the function
% to print an error and return linehist = -1 (scalar) and linestats = [-1 -1
-1].
%-----
-----

%% Check input arguments =====
s = size(llengths);
if s(1) < s(2)
    llengths=llengths';
end
s=size(llengths);

if s(2) ~= 1
    fprintf('Input data must be a vector, not a matrix\n');
    linehist = single(-1);
    linestats = [-1 -1 -1];
    return
end

s=size(minl);
if ~all(s == [1 1])
    fprintf('Please use a scalar for min line length\n');
    linehist = single(-1);
    linestats = [-1 -1 -1];
    return;
end

if mod(minl,1) ~= 0
    fprintf('Please use integer min line length\n');
    linehist = single(-1);
    linestats = [-1 -1 -1];
    return;
end

```

```

if minl <= 0
    minl = 1;
end

%% Begin computations
=====

ll=length(llengths);
if min(llengths) == max(llengths)
    % fprintf('Only one line length found\n');
    if llengths(1) >= minl
        linehist = single([llengths(1) ll]);
        linestats = [double(llengths(1)) 0 1];
    else
        linehist = single(0);
        linestats = [0 0 0];
    end
    return;
end
llengths = sort(llengths);

%% Find first observed line length >= minimum line length
x2 = [];
for i = 1:ll
    if llengths(i) >= minl
        x2 = llengths(i);
        i_first = i;
        break;
    end
end

%% Perform Calculations
if ~isempty(x2)
    %Do stats on the line lengths that are greater than minl
    ll_mean = mean(double(llengths(i_first:end)));
    ll_std = std(double(llengths(i_first:end)));
    ll_n = length(llengths(i_first:end));
    linestats = [ll_mean ll_std ll_n];

    %Do the histogram
    max_num_bins = llengths(end)-llengths(1)+1;
    x3 = zeros(max_num_bins,1,'single');
    lh2 = zeros(max_num_bins,1,'single');
    x3(1) = x2;
    nbins = 1;
    lh2(1) = 1;

    % Proceed from there
    for j = i+1:ll
        if llengths(j) == x3(nbins)
            lh2(nbins) = lh2(nbins)+1;
        else
            nbins = nbins + 1;
            x3(nbins)=llengths(j);
            lh2(nbins)=1;
        end
    end
end

```

```

        end

        x3 = x3(1:nbins);
        lh2 = lh2(1:nbins);
        linehist = [x3 lh2];

    else
        linehist = single(0);
        linestats = [0 0 0];
    end

    return

function entropy = xRQA_entropy(distr,nstates);

%*****
%*****
% FUNCTION entropy = xrqa_entropy(distr,nstates);
%
% Compute Shannon entropy of a distribution
%
% Input
%   distr -- distr vector, either column or row. All elements
%           are considered to be part of the distribution.
%   nstates -- number of possible states
%
% Output
%   entropy -- 1X2 vector containing shannon entropy &
%             max entropy possible given nstates - shannon entropy =
%             information according to Layzer 1988
%
% Example:
% my_entropy = xrqa_entropy(my_distr, 234);
%
% where my_distr is your distribution vector.
%
% Note: any errors in the input arguments causes the function
% to print an error and return entropy = -1 (scalar).
%-----
-----

%% Check input argument
s=size(distr);
if s(1) < s(2)
    distr=distr';
end

s=size(distr);
if s(2) ~= 1
    fprintf('Input data must be a vector, not a matrix\n');
    entropy = -1;
    return
end

s=size(nstates);
if ~all(s == [1 1])

```

```

        fprintf('Please use a scalar for number of states\n');
        entropy = -1;
        return;
    end

    if mod(nstates,1) ~= 0
        fprintf('Please enter integer number of states\n');
        entropy = -1;
        return;
    end

    if nstates <= 0
        fprintf('Number of states must be > 0\n');
        entropy = -1;
        return;
    end

    %% Compute
    distr2 = distr/sum(distr);
    ld = length(distr2);
    sumdist = 0;
    for i = 1:ld
        if distr2(i) ~= 0
            sumdist = sumdist - distr2(i)*log2(distr2(i));
        end
    end
    maxen = log2(nstates);
    entropy = [sumdist maxen-sumdist];

    return

function [td, rs, mats, err_code] = xRQA_stats(d,rescale,rad,tmin,minl)

%*****
%*****
% FUNCTION [td, rs, mats, err_code] = xRQA_stats(d,rescale,rad,tmin,minl);
%
% Calls the functions that perform RQA computations on a distance matrix.
%
% Inputs
%   d -- distance matrix (from xrqa_dist or mrqa_dist)
%   region -- 1 = use entire distance matrix anything else = use "diamond"
%   rescale -- rescale option (1=mean 2=max other=abs)
%   rad -- threshold radius (depends on rescale option)
%   tmin -- minimum recurrence time (samples) (the "Theiler window")
%   minl -- minimum line length (samples) for determinism, histogram,
entropy, & complexity
%
% Outputs
%   rs -- structure containing the RQA stats
%   mats -- structure containing the big matrices (threshold distance, etc.)
%-----
-----

%% Threshold the distance matrix =====
fprintf('Doing the thresholding...\n');

```



```

td = xRQA_radius(d,rescale,rad,tmin); %Threshold the distance matrix
if td == -1
    fprintf('Error in thresholding ');
    err_code = 1;
    rs = 0;
    mats = 0;
    return
end

%% Find all lines & compute TRENDS
=====
[ll,maxl_poss,npts,trend1,trend2] = xRQA_line(td,tmin);
if ll == -1
    fprintf('\nError in line counting\n');
    err_code = 2;
    rs = 0;
    mats = 0;
    return
end

%% LL histogram =====
fprintf('Histogramming the line lengths...\n');
[lh,llmsd] = xRQA_histlines(ll,minl); %Compute histogram of line lengths
if lh == -1
    fprintf('Error in creating histograms\n');
    err_code = 3;
    rs = 0;
    mats = 0;
    return
end
%lh is histogram of lines >= minl only
%llmsd = mean, SD, and N of lines >= minl only

%% ENTROPY of LL distribution =====
if lh ~= 0
    entropy = xRQA_entropy(double(lh(:,2)),maxl_poss-minl+1); %Compute
entropy of line length histogram
    if entropy == -1
        fprintf('Error in computing entropy\n');
        err_code = 4;
        rs = 0;
        mats = 0;
        return
    end
else
    entropy = [0 0];
end

%% Percent recurrence (%RECUR) =====
recur = sum(ll);
perc_rec = 100*recur/npts;

%% DETER, MAXLINE, algorithmic complexity of LL distribution =====
if lh ~= 0
    perc_determ = 100*sum(double(lh(:,1)).*double(lh(:,2)))/recur; % %DETER;
double-precision arithmetic required

```

```

        maxl_found = max(lh(:,1)); % Maximum diagonal line found (MAXLINE)
    else
        perc_determ = 0;
        maxl_found = 0;
    end

    %% Output to structures
    =====
    ==
    rs = struct('rescale',rescale, 'rad',rad, 'tmin',tmin, 'minl',minl, ...
        'perc_recur',perc_rec, 'perc_determ',perc_determ, 'npts',npts, ...
        'entropy',entropy, 'maxl_poss',maxl_poss, 'maxl_found',maxl_found, ...
        'trend1',trend1, 'trend2',trend2, 'llmnsd',llmnsd);

    mats = struct('rescale',rescale, 'rad',rad, 'tmin',tmin, 'minl',minl, ...
        'td',td, 'll',ll, 'lh',lh );

    err_code = 0;

    return;

```

Literature Cited

- [1] Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, et al. Incidence and Prevalence of Multiple Sclerosis in the Americas: A Systematic Review. *Neuroepidemiology*. 2013;40:195-210.
- [2] Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372:1502-17.
- [3] Cattaneo D, De Nuzzo C, Fascia T, Macalli M, Pisoni I, Cardini R. Risks of falls in subjects with multiple sclerosis. *Archives of physical medicine and rehabilitation*. 2002;83:864-7.
- [4] Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil*. 2009;23:259-69.
- [5] Kavanagh JJ, Morrison S, Barrett RS. Coordination of head and trunk accelerations during walking. *European journal of applied physiology*. 2005;94:468-75.
- [6] Huisinga JM, St George RJ, Spain R, Overs S, Horak FB. Postural response latencies are related to balance control during standing and walking in patients with multiple sclerosis. *Archives of physical medicine and rehabilitation*. 2014;95:1390-7.
- [7] Cameron MH, Horak FB, Herndon RR, Bourdette D. Imbalance in multiple sclerosis: a result of slowed spinal somatosensory conduction. *Somatosens Mot Res*. 2008;25:113-22.
- [8] Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. *Current neurology and neuroscience reports*. 2011;11:507-15.
- [9] Mancini M, Horak FB. The relevance of clinical balance assessment tools to differentiate balance deficits. *Eur J Phys Rehabil Med*. 2010;46:239-48.
- [10] Huisinga JM, Mancini M, St George RJ, Horak FB. Accelerometry reveals differences in gait variability between patients with multiple sclerosis and healthy controls. *Annals of biomedical engineering*. 2013;41:1670-9.
- [11] Mancini M, Carlson-Kuhta P, Zampieri C, Nutt JG, Chiari L, Horak FB. Postural sway as a marker of progression in Parkinson's disease: A pilot longitudinal study. *Gait & posture*. 2012;36:471-6.
- [12] Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility Lab to Assess Balance and Gait with Synchronized Body-worn Sensors. *Journal of bioengineering & biomedical science*. 2011;Suppl 1:007.
- [13] Kavanagh J, Barrett R, Morrison S. The role of the neck and trunk in facilitating head stability during walking. *Experimental brain research*. 2006;172:454-63.
- [14] Kavanagh JJ, Barrett RS, Morrison S. Age-related differences in head and trunk coordination during walking. *Human movement science*. 2005;24:574-87.
- [15] Adamczyk PG, Kuo AD. Redirection of center-of-mass velocity during the step-to-step transition of human walking. *The Journal of experimental biology*. 2009;212:2668-78.
- [16] Kuo AD. Stabilization of Lateral Motion in Passive Dynamic Walking. *THE INTERNATIONAL JOURNAL OF ROBOTICS RESEARCH*. 1991.
- [17] Kaipust JP, Huisinga JM, Filipi M, Stergiou N. Gait variability measures reveal differences between multiple sclerosis patients and healthy controls. *Motor control*. 2012;16:229-44.
- [18] Socie MJ, Motl RW, Pula JH, Sandroff BM, Sosnoff JJ. Gait variability and disability in multiple sclerosis. *Gait & posture*. 2013;38:51-5.
- [19] Saunders Jb Fau - Inman VT, Inman Vt Fau - Eberhart HD, Eberhart HD. The major determinants in normal and pathological gait. 1953.
- [20] Bruijn SM, Meijer OG, Beek PJ, van Dieen JH. Assessing the stability of human locomotion: a review of current measures. *Journal of the Royal Society, Interface / the Royal Society*. 2013;10:20120999.
- [21] Liu J, Zhang X, Lockhart TE. Fall risk assessments based on postural and dynamic stability using inertial measurement unit. *Safety and health at work*. 2012;3:192-8.

- [22] Lockhart TE, Liu J. Differentiating fall-prone and healthy adults using local dynamic stability. *Ergonomics*. 2008;51:1860-72.
- [23] Toebes MJ, Hoozemans MJ, Furrer R, Dekker J, van Dieen JH. Local dynamic stability and variability of gait are associated with fall history in elderly subjects. *Gait & posture*. 2012;36:527-31.
- [24] Kuo AD, Donelan JM. Dynamic Principles of Gait and Their Clinical Implications. *Physical Therapy*. 2010;90:157-74.
- [25] Dean JC, Alexander NB, Kuo AD. The effect of lateral stabilization on walking in young and old adults. *IEEE transactions on bio-medical engineering*. 2007;54:1919-26.
- [26] Bauby CE, Kuo AD. Active control of lateral balance in human walking. *Journal of biomechanics*. 2000;33:1433-40.
- [27] Schragger MA, Kelly VE, Price R, Ferrucci L, Shumway-Cook A. The effects of age on medio-lateral stability during normal and narrow base walking. *Gait & posture*. 2008;28:466-71.
- [28] Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. *The New England journal of medicine*. 2006;354:942-55.
- [29] Boes MK, Sosnoff JJ, Socie MJ, Sandroff BM, Pula JH, Motl RW. Postural control in multiple sclerosis: effects of disability status and dual task. *J Neurol Sci*. 2012;315:44-8.
- [30] Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. 1997.
- [31] Brady RA, Peters BT, Bloomberg JJ. Strategies of healthy adults walking on a laterally oscillating treadmill. *Gait & posture*. 2009;29:645-9.
- [32] Hurt CP, Rosenblatt N, Crenshaw JR, Grabiner MD. Variation in trunk kinematics influences variation in step width during treadmill walking by older and younger adults. *Gait & posture*. 2010;31:461-4.
- [33] Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. *Gait & posture*. 2003;18:1-10.
- [34] Kavanagh JJ, Menz HB. Accelerometry: a technique for quantifying movement patterns during walking. *Gait & posture*. 2008;28:1-15.
- [35] Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Movement disorders : official journal of the Movement Disorder Society*. 2013;28:1544-51.
- [36] Latt MD, Menz HB, Fung VS, Lord SR. Walking speed, cadence and step length are selected to optimize the stability of head and pelvis accelerations. *Experimental brain research*. 2008;184:201-9.
- [37] Ralston HJ. Energy-speed relation and optimal speed during level walking. *Int Z Angew Physiol*. 1958;17:277-83.
- [38] Hoogkamer W, Potocanac Z, Duysens J. Quick foot placement adjustments during gait: direction matters. *Experimental brain research*. 2015.
- [39] Crenshaw JR, Rosenblatt NJ, Hurt CP, Grabiner MD. The discriminant capabilities of stability measures, trunk kinematics, and step kinematics in classifying successful and failed compensatory stepping responses by young adults. *Journal of biomechanics*. 2012;45:129-33.
- [40] Winter DA. Human balance and posture control during standing and walking. *Gait & posture*. 1995;3:193-214.
- [41] Moe-Nilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. *Journal of biomechanics*. 2004;37:121-6.
- [42] Moe-Nilssen R, Helbostad JL. Interstride trunk acceleration variability but not step width variability can differentiate between fit and frail older adults. 2005.
- [43] Bruijn SM, Ten Kate WR, Faber GS, Meijer OG, Beek PJ, van Dieen JH. Estimating dynamic gait stability using data from non-aligned inertial sensors. *Annals of biomedical engineering*. 2010;38:2588-93.

- [44] Orendurff MS, Segal AD, Klute GK, Berge JS, Rohr ES, Kadel NJ. The effect of walking speed on center of mass displacement. *J Rehabil Res Dev*. 2004;41:829-34.
- [45] Lugade V, Lin V, Chou LS. Center of mass and base of support interaction during gait. *Gait & posture*. 2011;33:406-11.
- [46] Menz HB, Lord SR, Fitzpatrick RC. Age-related differences in walking stability. *Age and ageing*. 2003;32:137-42.
- [47] Brodie MA, Menz HB, Lord SR. Age-associated changes in head jerk while walking reveal altered dynamic stability in older people. *Experimental brain research*. 2014;232:51-60.
- [48] Tesio L, Rota V, Chessa C, Perucca L. The 3D path of body centre of mass during adult human walking on force treadmill. *Journal of biomechanics*. 2010;43:938-44.
- [49] Menz HB, Lord SR, Fitzpatrick RC. Acceleration patterns of the head and pelvis when walking are associated with risk of falling in community-dwelling older people. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2003;58:M446-52.
- [50] Waters RL, Morris J, Perry J. Translational motion of the head and trunk during normal walking. *Journal of biomechanics*. 1973;6:167-72.
- [51] Kavanagh JJ, Barrett RS, Morrison S. Upper body accelerations during walking in healthy young and elderly men. *Gait & posture*. 2004;20:291-8.
- [52] Keshner F, Peterson B. Mechanisms controlling human head stabilization. I. Head-neck dynamics during random rotations in the horizontal plane. *Journal of neurophysiology*. 1995;73:2293-301.
- [53] Menz HB, Lord SR, Fitzpatrick RC. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. *Gait & posture*. 2003;18:35-46.
- [54] Corporaal SH, Gensicke H, Kuhle J, Kappos L, Allum JH, Yaldizli O. Balance control in multiple sclerosis: correlations of trunk sway during stance and gait tests with disease severity. *Gait & posture*. 2013;37:55-60.
- [55] Holt KJ, Jeng Sf Fau - Rr RR, Rr Rr Fau - Hamill J, Hamill J. Energetic Cost and Stability During Human Walking at the Preferred Stride Velocity. 2003.
- [56] Kang HG, Dingwell JB. Dynamic stability of superior vs. inferior segments during walking in young and older adults. *Gait & posture*. 2009;30:260-3.
- [57] Beurskens R, Wilken JM, Dingwell JB. Dynamic stability of superior vs. inferior body segments in individuals with transtibial amputation walking in destabilizing environments. *Journal of biomechanics*. 2014;47:3072-9.
- [58] Rosenblatt NJ, Hurt CP, Latash ML, Grabiner MD. An apparent contradiction: increasing variability to achieve greater precision? *Experimental brain research*. 2014;232:403-13.
- [59] Stergiou N, Harbourne R, Cavanaugh J. Optimal movement variability: a new theoretical perspective for neurologic physical therapy. *Journal of neurologic physical therapy : JNPT*. 2006;30:120-9.
- [60] Dingwell JB, Cusumano JP. Nonlinear time series analysis of normal and pathological human walking. *Chaos (Woodbury, NY)*. 2000;10:848-63.
- [61] Latt MD, Menz HB, Fung VS, Lord SR. Acceleration patterns of the head and pelvis during gait in older people with Parkinson's disease: a comparison of fallers and nonfallers. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2009;64:700-6.
- [62] Stergiou N, Decker LM. Human movement variability, nonlinear dynamics, and pathology: is there a connection? *Human movement science*. 2011;30:869-88.
- [63] Tochigi Y, Segal NA, Vaseenon T, Brown TD. Entropy analysis of tri-axial leg acceleration signal waveforms for measurement of decrease of physiological variability in human gait. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 2012;30:897-904.
- [64] Harbourne RT, Stergiou N. Movement Variability and the Use of Nonlinear Tools: Principles to Guide Physical Therapist Practice. *Physical Therapy*. 2009;89:267-82.

- [65] Dingwell JB, Kang HG. Differences between local and orbital dynamic stability during human walking. *Journal of biomechanical engineering*. 2007;129:586-93.
- [66] Dingwell JB, Marin LC. Kinematic variability and local dynamic stability of upper body motions when walking at different speeds. *Journal of biomechanics*. 2006;39:444-52.
- [67] England SA, Granata KP. The influence of gait speed on local dynamic stability of walking. *Gait & posture*. 2007;25:172-8.
- [68] Terrier P, Reynard F. Effect of age on the variability and stability of gait: a cross-sectional treadmill study in healthy individuals between 20 and 69 years of age. *Gait & posture*. 2015;41:170-4.
- [69] Kavanagh JJ. Lower trunk motion and speed-dependence during walking. *Journal of neuroengineering and rehabilitation*. 2009;6:9.
- [70] Granata KP, Lockhart TE. Dynamic stability differences in fall-prone and healthy adults. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology*. 2008;18:172-8.
- [71] Cavanaugh JT, Mercer VS, Stergiou N. Approximate entropy detects the effect of a secondary cognitive task on postural control in healthy young adults: a methodological report. *Journal of neuroengineering and rehabilitation*. 2007;4:42.
- [72] Bisi MC, Riva F, Fau - Stagni R, Stagni R. Measures of gait stability: performance on adults and toddlers at the beginning of independent walking.
- [73] Riva F, Toebe Mj, Fau - Pijnappels M, Pijnappels M, Fau - Stagni R, Stagni R, Fau - van Dieen JH, van Dieen JH. Estimating fall risk with inertial sensors using gait stability measures that do not require step detection. 2013.
- [74] Li K, Li Z-M. Cross recurrence quantification analysis of precision grip following peripheral median nerve block. *Journal of neuroengineering and rehabilitation*. 2013;10:28-.
- [75] Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A*. 1991;88:2297-301.
- [76] Wolf A, Swift JB, Swinney HL, Vastano JA. Determining Lyapunov exponents from a time series. *Physica D: Nonlinear Phenomena*. 1985;16:285-317.
- [77] Mees AI, Judd K. Dangers of geometric filtering. *Physica D: Nonlinear Phenomena*. 1993;68:427-36.
- [78] Kaffashi F, Foglyano R, Wilson CG, Loparo KA. The effect of time delay on Approximate & Sample Entropy calculations. *Physica D: Nonlinear Phenomena*. 2008;237:3069-74.
- [79] Cellucci CJ, Albano AM, Rapp PE. Statistical validation of mutual information calculations: Comparison of alternative numerical algorithms. *Physical Review E*. 2005;71:066208.
- [80] Yentes J, Hunt N, Schmid K, Kaipust J, McGrath D, Stergiou N. The Appropriate Use of Approximate Entropy and Sample Entropy with Short Data Sets. *Annals of biomedical engineering*. 2013;41:349-65.
- [81] Kennel MB, Brown R, Abarbanel HD. Determining embedding dimension for phase-space reconstruction using a geometrical construction. *Physical review A*. 1992;45:3403.
- [82] Richardson D, Dale R, Shockley K. Synchrony and swing in conversation: Coordination, temporal dynamics, and communication. *Embodied communication in humans and machines*. 2008:75-94.
- [83] Takacs J, Kirkham AA, Perry F, Brown J, Marriott E, Monkman D, et al. Lateral trunk lean gait modification increases the energy cost of treadmill walking in those with knee osteoarthritis. *Osteoarthritis and Cartilage*. 2014;22:203-9.
- [84] DeLisa JA, Scientific USVHA, Section TP. *Gait Analysis in the Science of Rehabilitation: Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service, Scientific and Technical Publications Section*; 1998.
- [85] Mazza C, Iosa M, Pecoraro F, Cappozzo A. Control of the upper body accelerations in young and elderly women during level walking. *Journal of neuroengineering and rehabilitation*. 2008;5:30.

- [86] Cattaneo D, Carpinella I, Aprile I, Prosperini L, Montesano A, Jonsdottir J. Comparison of upright balance in stroke, Parkinson and multiple sclerosis. *Acta Neurol Scand*. 2015.
- [87] Riley PO, Paolini G, Della Croce U, Paylo KW, Kerrigan DC. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait & posture*. 2007;26:17-24.
- [88] O'Connor SM, Kuo AD. Direction-dependent control of balance during walking and standing. *Journal of neurophysiology*. 2009;102:1411-9.
- [89] Hoogkamer W, Bruijn SM, Sunaert S, Swinnen SP, Van Calenbergh F, Duysens J. Toward new sensitive measures to evaluate gait stability in focal cerebellar lesion patients. *Gait & posture*. 2015.
- [90] Labini FS, Meli A, Ivanenko YP, Tufarelli D. Recurrence quantification analysis of gait in normal and hypovestibular subjects. *Gait & posture*. 2012;35:48-55.
- [91] Dingwell JB, Robb RT, Troy KL, Grabiner MD. Effects of an attention demanding task on dynamic stability during treadmill walking. *Journal of neuroengineering and rehabilitation*. 2008;5:12.
- [92] Owings TM, Grabiner MD. Step width variability, but not step length variability or step time variability, discriminates gait of healthy young and older adults during treadmill locomotion. *Journal of biomechanics*. 2004;37:935-8.
- [93] Rosenblatt NJ, Grabiner MD. Measures of frontal plane stability during treadmill and overground walking. *Gait & posture*. 2010;31:380-4.